ANNALS OF
INTERNAL MEDICINE

VOLUME 18 MAY, 1943 NUMBER 5

CANCER OF THE STOMACH: WITH SPECIAL REFERENCE TO EARLY DIAGNOSIS *

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THE small percentage of five year survivals following operative intervention in cases of carcinoma of the stomach has been very discouraging. The aim of all diagnostic methods has, therefore, been to establish an early diagnosis. Nevertheless, only between 30 and 40 per cent of cases of resectable cancer of the stomach are submitted to the surgeon. Patients with cancer who never reach the operating table are in one of two categories. The cancer is either of such a malignant nature that it spreads very rapidly to the neighboring glands and organs, or to distant structures; or the growth has invaded a silent area of the stomach, remaining asymptomatic. Such a patient presents himself for treatment when the lesion has already reached an inoperable stage.

From our clinical experience, it seems appropriate to divide cancer of the stomach into two groups. The first group comprises those cases in which the cancer starts on a perfectly healthy gastric mucous membrane. In the second group the cancer develops on a previously diseased mucous membrane.

In the first group are approximately 70 per cent of all the cases. In reality, the patient will often volunteer the information that he has had an iron clad stomach and could digest everything. Though most of these patients are above the age of 50, the cancer may occur in younger individuals, and even before the age of 20. The younger the individual, the more malignant the growth.

When the cancer affects the silent area of the stomach (the greater curvature of the pars media or the lesser curvature) involving more of the anterior wall than the posterior wall, gastric motility is usually not interfered with. Consequently the patient does not present himself until a good sized palpable mass can be detected in the epigastrium. The subjective symptoms are extremely vague, consisting of epigastric distress, belching,

* Received for publication February 19, 1942.

fullness in the epigastrium, loss of appetite, coated tongue and dryness of the mouth. There may be only moderate loss of weight, especially if the symptoms are of a few weeks' duration. Gastric acidity may be normal, although occasionally there is sub- or even anacidity. Normal acidity should not in-

FIG. 1. Hour glass stomach due to carcinoma of the pars media.

fluence the diagnosis. In younger individuals, particularly in the rare cases of cancer of the stomach occurring before the age of 30, all the clinical evidence of cancer can exist despite a perfectly normal acidity.

When the cancerous lesion involves the posterior wall of the pars media, pain in the epigastrium radiating to the back is a prominent symptom. The

pain is often excruciating, and is worse at night, necessitating the administration of narcotics. The greater the involvement of the posterior wall, the less accessible is the lesion to palpation.

If the cancer invades the entire anterior and posterior walls of the pars media, the characteristic cancer hour glass stomach is produced (figure 1).

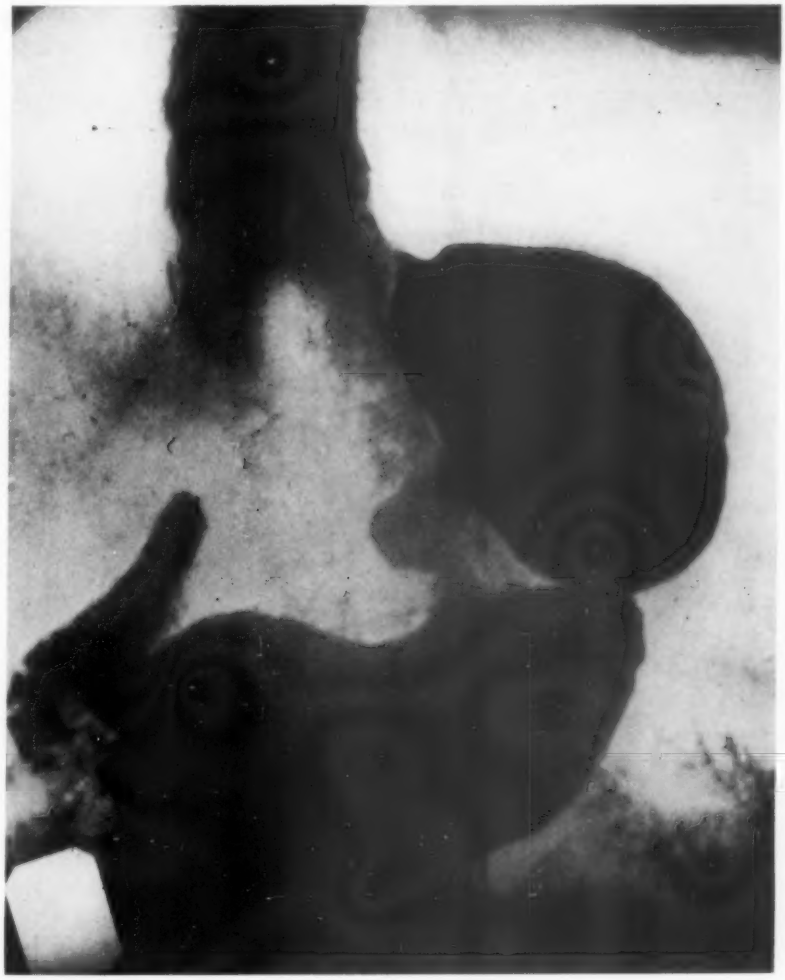

FIG. 2. Hour glass stomach due to ulcer on lesser curvature.

The edges of the constricted portion are irregular, and the canal between the upper and lower part of the hour glass is centrally situated, in contradistinction to the canal of hour glass due to ulcer (figure 2), in which case the connecting canal is on a line with the lesser curvature of the stomach. Furthermore, as seen in the figures, in cancer hour glass stomach the upper sac fills only partially with barium and, therefore, is smaller than the lower

sac which is more completely filled. This is due to the rigidity of the canal which permits the barium to rush through. On the other hand, in the ulcer hour glass, the connecting canal between the two sacs is usually spastic and inhibits passage of the barium meal. The upper sac, therefore, contains the greater part of the barium meal. In some cases in which there is a stenosing ulcer of the pylorus and an ulcer of the lesser curvature of the stomach, the hour glass will show the lower sac to be half-moon shaped and larger than the upper sac (figure 3).

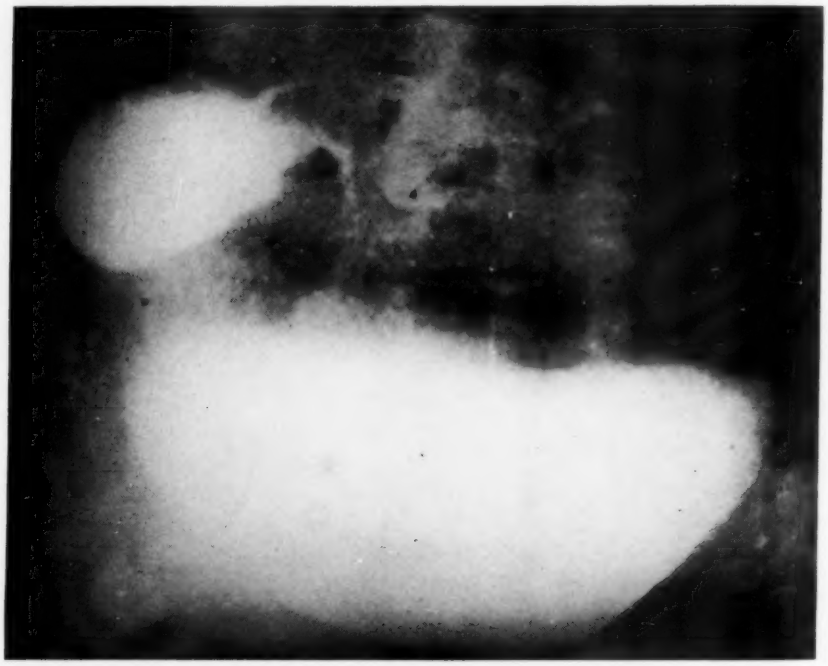

FIG. 3. Stenosing ulcer of pylorus and ulcer of lesser curvature, producing hour glass stomach, the lower sac half-moon shaped. (Stomach photographed from left to right.)

If the cancer develops at the next most common site, namely at the prepyloric region, and if it is not the rare annular type which invades the lumen of the pylorus, motility disturbances are absent. Such patients have insufficient subjective symptoms to present themselves for early treatment. When seen they have a large, tender, freely movable, palpable tumor in the epigastric region, and to the right of the median line. In these cases there is subacidity or anacidity.

Cancer of the pyloric region usually develops later in life than does cancer of the pars media, and is often very insidious in onset. The symptoms are very vague, consisting primarily of loss of appetite, with a marked dislike for meats. A patient in his late forties or fifties who previously had no digestive disturbances, presenting himself with such symptoms, even if the acidity is normal, should be subjected to a very careful roentgenologic

and gastroscopic examination in order that the cancer in its earliest stage should not be overlooked.

The rapid passage of food into the duodenum visualized roentgenologically is an important finding in early cases of pyloric cancer. The pylorus presents a rigid tube which, however, is not irregular, so that unless the roentgenologist knows the clinical history, he may be unable to make a diagnosis of cancer from the roentgen-ray examination alone. We adhere to the teaching of Holzknecht [1] as to the diagnosis of a scirrhous carcinoma of the pylorus in previously healthy middle aged or elderly individuals. The essence of his observations as early as 1910 is the following: The outstanding symptoms leading to such a diagnosis are subacidity or anacidity, a rigid pylorus through which food passes with extraordinary rapidity in the early part of digestion, incomplete emptying of the stomach after four or five hours, and diminished or absent peristaltic waves in the pyloric region and a conspicuous absence of antral contraction. We are in accord with Holzknecht that such cases should be given the benefit of surgical intervention. It is quite true that occasionally this type of pylorus might be due to a chronic pyloritis, so that resection may only reveal the presence of an inflammatory lesion, but in the majority of cases one is rewarded by having diagnosed cancer in the resectable stage.

The rapid passage of food during the early part of digestion is due to the fact that the sphincter pylori has not been invaded by the lesion and is patent. This may be compared to carcinoma of the rectum in which case the sphincter ani acts in a similar manner, or to cancer in the lower end of the esophagus in which passage of food into the stomach is not disturbed although there is accumulation of food in the esophagus proper and dilatation of the esophagus due to atony of the organ.

Disturbed motility is an early phenomenon if the lumen of the pylorus is invaded by an annular carcinoma. Subacidity is the rule, and lactic acid is also present if there is marked gastric stasis. Epigastric pain, relieved by spontaneous or induced vomiting, is frequent in these cases (figure 4).

Occasionally the cancer invades exclusively the posterior wall and lesser curvature of the stomach. Characteristic symptoms are: persistent pain in the lower dorsal and epigastric region, frequent vomiting of bile stained gastric secretions, regurgitation of gastric secretions into the esophagus and mouth causing burning in the epigastric region and behind the sternum, persistent dryness of the throat and tongue which is frequently fissured. The pain and regurgitation are aggravated when the patient lies on his back, so that he seeks a comfortable position for relief of these symptoms. In most of these instances the cancer is a slowly growing scirrhous type and the roentgenological evidence reveals a rigid pars media, absence of peristalsis, and occasionally actual deformity of the pars media.

A rarer site of cancer of the stomach is the cardia. Deglutition disturbance is the earliest symptom, and cardiospasm is always present. It may be extremely difficult at times to detect the cancer roentgenologically.

No effort should be spared in this direction. Films should be taken in every possible position, namely, standing, recumbent, supine, right and left oblique and particularly in the Levy-Dorn position, i.e., with the patient in the supine position, buttocks elevated, the rays directed to the cardiac end. It is of great importance that every effort should be made to visualize the air bubble. Deformity of the air bubble is an important sign in cancer of that location. If the air bubble is not visualized, it is advisable to give the patient a Seidlitz

FIG. 4. Annular carcinoma of pylorus showing obstruction.

powder, and within two to five minutes, to take another roentgenogram. This often facilitates the roentgenological visualization of the air bubble. If the aspirated contents by stomach tube show an excess of blood, particularly old blood, it is of diagnostic importance. Esophagoscopy and gastroscopy are of diagnostic aid. Recent surgical advances for cancer in this region [14] have facilitated more satisfactory treatment of this type of lesion than in the past and may extend the opportunity for favorable life expectancy. We know from experience that many of these cases are looked upon as nervous cardiospasm. During the time that elapses without any interven-

tion, avitaminosis and dehydration usually result, so that the poor condition of the patient renders surgery impossible.

Another site for a slowly developing carcinoma is the entire posterior wall of the stomach without invasion of the anterior wall or curvatures, in which the roentgenogram is negative and no mass is palpable. Only gastroscopic examination with a biopsy can establish the diagnosis. Pain in the upper abdomen independent of meals is the most striking symptom, but the diagnosis may be overlooked for months or even years because of the negative findings. Early gastroscopic examination in these cases is, therefore, urgent.

Scirrhous carcinoma of the entire stomach, or a "leather bottle stomach" roentgenologically, the stomach appearing as a narrow, rigid tube, is another rare and slowly growing malignancy. The stomach is transversely placed, well above the umbilicus. Fluoroscopically, the barium is seen to pass through so rapidly that within a half or three-quarters of an hour, the entire stomach is empty. The air bubble is very small or entirely absent. The fundus is either absent or very small. Often the barium is regurgitated into the esophagus, and the esophagus and stomach appear as two tubes (figure 5)—a vertical (esophagus) connecting with a transverse (stomach) tube. The lesion is frequently called linitis plastica. Because of its slowness of growth, it acts almost like a benign lesion, yet its eventual outcome is that of any slowly growing carcinoma. These cases have complete absence of HCl and ferments (achylia).

We have dwelt in detail on the slowly growing types of cancer that develop on a healthy gastric mucous membrane. They should be subjected to surgery even if a large palpable mass is present because there is no tendency to early metastasis. Although radical surgery is necessary, with a mortality as high as 10 to 15 per cent, if the operation is successful, lasting and good results may be expected. Without operative intervention it must be remembered that the mortality is 100 per cent.

It is very difficult to foretell the percentage of five year survivals or even cures in the above groups of cases, but it may be said that in the absence of metastases, and with a successful operation, the patient can go on for many years without recurrence. In these cases the presence of a marked secondary anemia should not deter one from surgical intervention provided there is adequate preoperative preparation. When there has been prolonged obstruction and marked atony of the stomach one should resort to gastric lavage for 10 to 12 days preceding operation. If the patient is very weak, it may be advisable to do a two stage operation, i.e. gastroenterostomy followed by a resection about one month later.

The medullary form of carcinoma of the stomach usually arises on a previously healthy mucous membrane, grows very rapidly and has a tendency to early metastases. The metastases are through the lymphatics, mainly to the neighboring glands, and to the liver, but may also spread quickly to the peritoneum and to the pouch of Douglas. In rare instances metastases may

spread by way of the blood to distant organs. In the early stage the growth in the liver consists of numerous small nodules. There is usually anemia

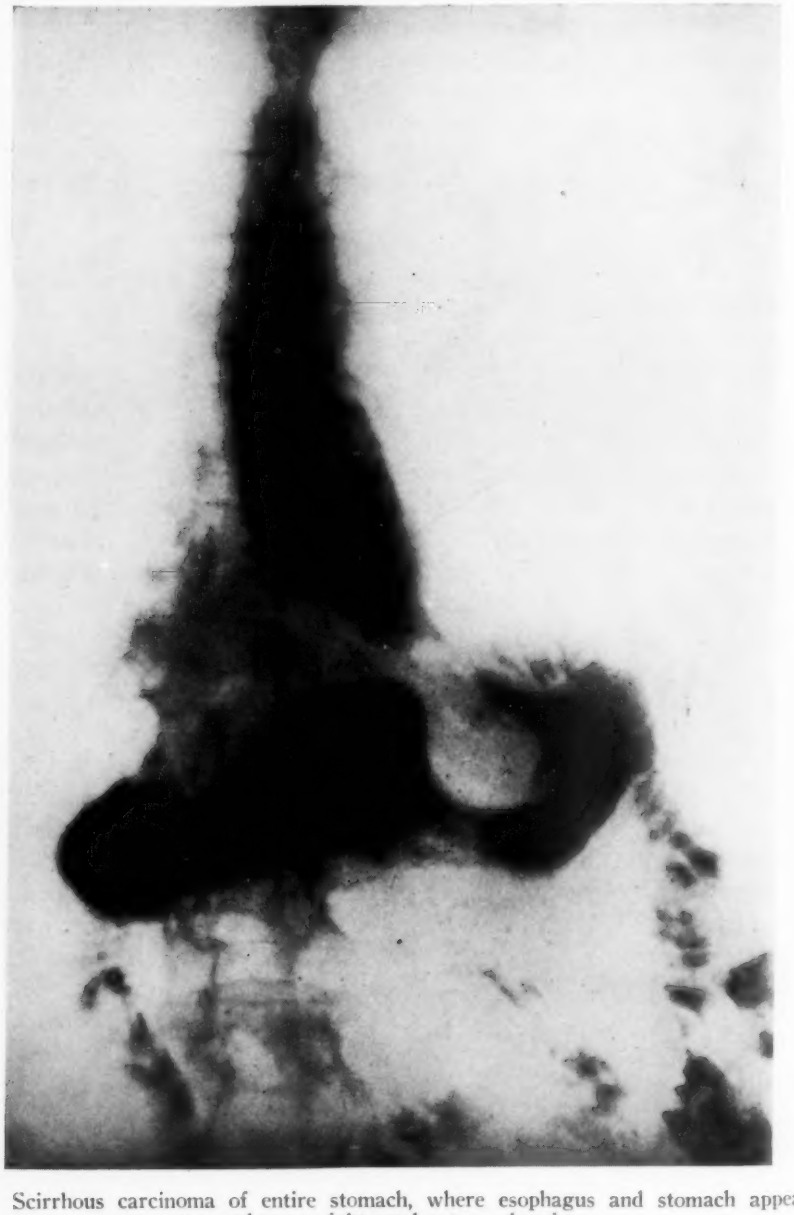

FIG. 5. Scirrhous carcinoma of entire stomach, where esophagus and stomach appear as two tubes at right angles to each other.

varying in degree. The symptoms are gastric distress, rapid loss of appetite, loss of weight, occasional epigastric pain and early evidence of cachexia. A palpable mass can be detected early in the epigastric region. Roentgen-ray

shows an eaten out pars media, extending to the pylorus (figure 6). If the liver is not very large and nodular, if there is no ascites and there is no rectal shelf, and jaundice is absent, it is advisable to prepare the patient carefully by blood transfusion for surgical intervention. It is well known that most surgeons, finding only a few nodules in the liver, may do a gastrectomy with removal of some of the glands. If the patient survives the operation, he may be comfortable for a year or even longer. However, the immediate

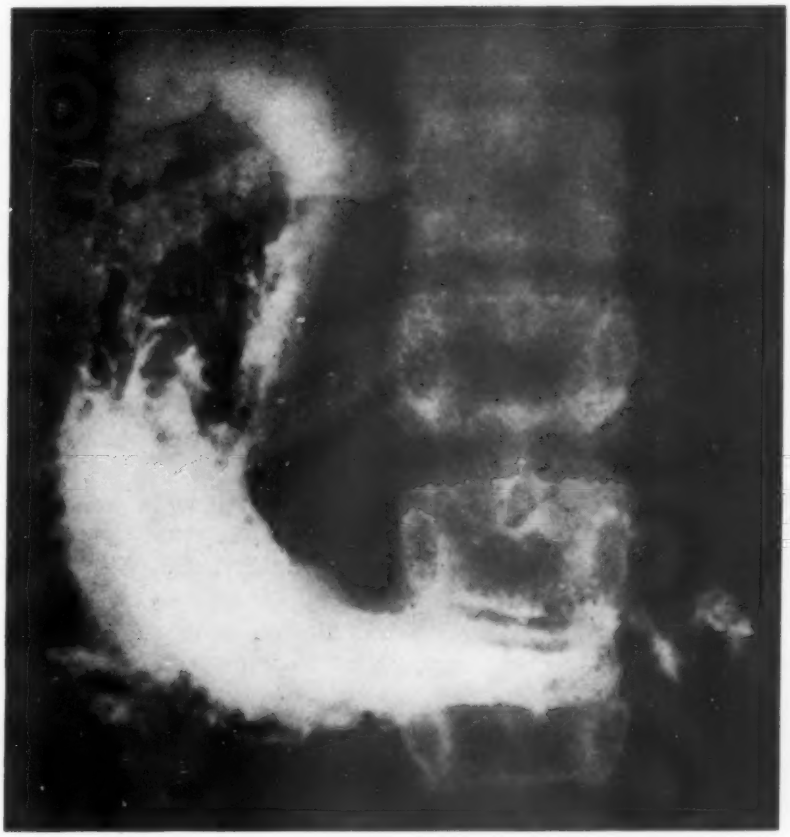

FIG. 6. Medullary carcinoma. (Stomach photographed from left to right.)

mortality may be as high as 30 to 40 per cent. We agree with A. A. Berg (personal communication) that the above cases are just as much entitled to prolongation of life and a comfortable existence as those patients whom the internist treats for renal disease with progressive uremia, or progressive heart failure, although the span of life will not be long.

Finally, there are cases, fortunately smaller in number, in which the metastases are mainly through the blood stream and partially through the lymphatics. The primary gastric growth is usually very small, at times no larger than a hazel nut. The local gastric symptoms are insignificant. The

patient may present himself with complaints of weakness, elevation of temperature, increased respirations. The physical signs in the lungs may be very meager, but the roentgen-ray examination of the chest shows evidence of lymphangitis carcinomatosis. In rare instances, metastases may be present in the brain, so that the symptoms may lead to an erroneous diagnosis of primary brain tumor. These cases, because of their widespread metastases, are not amenable to surgical intervention.

Of major importance in this discussion are the remaining 30 per cent of the cases in which the cancerous lesion develops on a previously diseased mucous membrane. This group comprises patients who have had gastric complaints for many years before cancer developed, and those in whom the growth of cancer is so slow, as shown by Eusterman [2] and others, that the lesion remains localized for several years.

The precancerous symptoms vary in nature and are usually very bizarre and noncharacteristic, and are, therefore, interpreted mostly as neurogenic. There are three separate groups of clinical entities on the soil of which the cancer develops: (1) gastritis, (2) polyps, and (3) gastric ulcer.

Gastritis. The most important group comprises cases of gastritis. The appreciation and absolute clinical establishment of this condition must be credited to the significant work of Schindler [3] and his co-workers. Schindler perfected the flexible gastroscope and was able to demonstrate that gastritis is by no means rare, and he showed that on the basis of gastritis, cancer may develop in some instances. His contribution is of extreme importance in that it made observers conscious that many cases which were interpreted as having functional disorders were in reality suffering from gastritis. Schindler furthermore called attention to the fact that if the symptoms become aggravated and the patient showed evidence of wasting, the gastroscope may establish the presence of early cancer before roentgen diagnosis is possible, thus enabling early surgical intervention and possibility of permanent cure.

In order to establish the diagnosis of primary gastritis we must evaluate its accompanying symptoms, especially since they are not characteristic. The patient usually has a very sensitive digestive apparatus, a capricious appetite, a coated tongue, a dry mouth, and pain is conspicuously absent. Upper abdominal distress which may persist for days or weeks is a very frequent symptom. Because of the chronicity of the condition, the patient becomes accustomed to the symptoms with the result that the loss of weight may be offset by a sufficient qualitative food intake. If there be an accidental error in diet, recurrence of symptoms usually results. The patient is constipated and persistent pyrosis may be present not only in the epigastrium but often behind the sternum. There is regurgitation of food or gastric secretion of disagreeable taste, and sometimes of an offensive odor. In most cases, the gastric secretions are qualitatively and even quantitatively affected. Subacidity is the rule, provoking the question as to whether there is diminution of actual secretion, or whether the normal gastric secretion is neu-

tralized by the excessive gastric mucus due to the presence of catarrh. In the vast majority of cases the latter condition exists, and is demonstrable by the aspirated gastric contents. Macroscopically there is a large quantity of mucus; microscopically, there are red and white cells in addition to mucous shreds.

Roentgen-ray studies of the mucous membrane show definite thickening of the gastric rugae and deposits of islands of barium varying in size and shape.

Patients with gastritis as a rule are not awakened by pain, as is the case in gall-bladder disease or peptic ulcer. In persistent true achylia there may be a tendency to loose bowel movements (gastrogenic diarrhea) and also poor digestion of meat, the latter explaining the presence of undigested meat fibers in the stools.

Schindler has stressed the fact that in all forms of gastritis, extragastric symptoms such as headache, nervousness, numbness and tingling of the fingers and toes may be present.

If such patients begin to show persistent and aggravated gastric digestive disturbances, they must be observed at regular intervals of three months by both gastroscopic and roentgenologic studies, in order to detect the presence of malignancy as early as possible. Both these studies are essential because even in the hands of the most skillful gastroscopist, one will encounter an occasional case in which the presence of a small carcinoma may escape detection. Roentgenologic evidence of stiffening of the pars media and pylorus or very active or complete absence of peristalsis of the pars media and pylorus, justifies surgical exploration. Schindler and many others state that it is very difficult to detect a small lesion high up in the fundus, gastroscopically, contrary to what one would expect. Early evidence of incomplete cardiospasm and deformity of the air bag, imperfect visualization of the cardiac end of the stomach and slight deformity of the same when films are taken in varying positions (as described above) may lead to earlier suspicion and even a diagnosis by roentgenogram. On the other hand, when a lesion is situated on the posterior wall of the pars media, especially if it is the slowly growing, flat carcinoma of the scirrhous type, only by use of the gastroscope can positive evidence in this early state be demonstrated. Roentgenologically, even considerable involvement of the posterior wall may escape detection.

Of vital importance from the practical point of view is cancer of the pyloric portion. Here both gastroscopic and roentgen examinations may at first be disappointing; but occasionally, at an early stage, although the pylorus may be regular in outline, it is narrower than normal, resembling pylorospasm. A narrowed pylorus in conjunction with anacidity is very suspicious of cancer. However, pylorospasm secondary to gall-bladder disease may also exist, as first pointed out by Holzknecht and Luger.[4] If pylorospasm persists, even though gastroscopic examination is negative, exploratory laparotomy is justifiable.

Polyps. There are two types of polyps, namely, the congenital and the acquired.

The congenital type may be single or multiple and pedunculated. The multiple congenital polyps are usually small. The single type may reach a large size. We have encountered a case in which the polyp was the size of a tangerine. These polyps are usually asymptomatic and are only accidentally discovered, either at postmortem examination, or roentgenologically by the appearance of negative circular shadows in the stomach. At times they bleed, and the large single polyp may give rise to uncontrollable hemorrhage which can be stopped only by operative intervention.

Of greater importance from the standpoint of the development of cancer is the acquired type of polyp. This originates on the basis of gastritis (gastritis polyposa). Gastroscopy and biopsy are the conclusive diagnostic methods and surgery is indicated if the findings warrant it.

Gastric Ulcer. Finally, we have the third group, gastric cancer on an ulcer basis. There is still a great deal of controversy and extreme divergence of opinion as to the frequency with which gastric ulcer eventually becomes malignant. The painstaking studies of Wilson and McCarty [5] of the Mayo Clinic on this subject were originally quoted as indicating between 60 and 70 per cent. The erroneous impression was created that in 60 or 70 per cent of ulcers a cancer developed. What they actually meant was that in 60 or 70 per cent of cancer cases there was a previous ulcer. They paid strict attention to the cytology of the lesion. If elongated and deformed cells (cytoplasia) were found in the base of the ulcer, it was considered malignant. Finsterer, who in great measure agrees with these observations, is of the opinion that the cytoplasia must involve the edges of the ulcer as well. Some pathologists, particularly keen observers like Aschoff [6] and Ewing,[7] do not share this opinion. The former states that the highest percentage he encountered on an ulcer basis was 2½ to 3 per cent, and furthermore, that, "cancer can frequently ulcerate, but an ulcer seldom cancerates." Ewing doubts completely the existence of cancer on an ulcer basis. Schindler is uncompromising in his opinion. He denies completely the occurrence of cancer on an ulcer basis.

It has been our experience with cases in which the history could be traced, that gastric ulcer has preceded the onset of cancer by a number of years. We stated in a previous communication [8] that it may occur in 2 to 3 per cent of the cases. It is rather striking that in a recent contribution, Walters [9] stated that in one-third of the cases operated on for cancer of the stomach, there had been ulcer symptoms. We have similarly encountered cases of proved clinical cancer, in which the symptoms were those of ulcer, although no ulcer ever existed.

In this group there are two subgroups, one in which ulcer actually preceded the development of cancer, and the second in which the cancer begins with ulcer symptoms, without the presence of ulcer. We wish to stress the fact that in both subgroups the symptoms of cancer develop gradually, the

lesion is more benign in its behavior and, therefore, more likely to be resectable, and the opportunities for prolonged or even permanent cures are more favorable. It is evident that we must analyze the symptoms and signs of such cases with great care.

In the first group, the subjective symptoms of peptic ulcer have existed for a great number of years. There is also definite evidence of ulcer roentgenologically, either in the form of a niche in the pars media or definite evidence of ulcer in the prepyloric area. These lesions may periodically appear or disappear, with corresponding changes in subjective symptoms. In those cases in which there is reason to suspect a change to malignancy, the subjective symptoms persist and are somewhat altered in character. Instead of pure hunger pain, there is a persistent gnawing pain in the epigastrium radiating to the spine. Even during the pain free intervals there is a persistent sensation of bloatedness. During the night the patient is distressed by distention and actual pain, and only slightly relieved by alkalies, or not at all. Milk, which always gave relief in the past, now gives distress. Pyrosis is persistent and extends into the esophagus. Appetite becomes markedly diminished. The tongue becomes coated. Loss of weight is out of proportion to the diminished food intake. Weakness and gradual anemia ensue. Anemia is invariably hypochromic and is due in the majority of cases to inanition and avitaminosis and in many instances is a result of persistent occult bleeding which is demonstrable in the stool or stomach contents. The physical examination may be entirely negative except for persistent tenderness in the pyloric or epigastric region. Examination of the gastric contents will show a tendency to subacidity. Examination of the fasting gastric secretion will invariably show microscopic and even macroscopic retention of food eaten the night before. This retention may be best studied by giving the patient eight or 10 raisins, currants, or a few plums the night before. We emphasize the importance of microscopic and macroscopic retention as an early sign of gastric motility disturbance in these cases at a time when the barium meal shows no disturbance in motility.

What are the roentgenological signs indicative of transformation of a benign ulcer to malignancy? Carman [10] expressed his view that an ulcer on the lesser curvature of the stomach with a niche having a diameter 2.5 cm. or more should be regarded as malignant and should be submitted to surgery. In his later studies, based on a great deal of experience roentgenologically and with postoperative specimens, he stated that ulcer niches that become malignant have special features, namely, they appear meniscus-shaped with the convexity towards the gastric wall and the concavity towards the lumen when viewed in profile. However, we have encountered cases in which the niche fulfilled the requirements for the diagnosis of malignancy as set down by Carman, yet the patient made a complete recovery after weeks of treatment, and continued well for many years.

Even before Carman described the size and meniscus niche as indicating carcinomatous degeneration of ulcer, two cases in our experience are worthy

of mention. The first was a male, about 43 years old, who had ulcer symptoms for many years. There was a niche on the lesser curvature 4 to 5 cm. in diameter, with considerable deformity of the pars media. At operation, Dr. Leo Buerger found that owing to the fact that the posterior wall was adherent to the pancreas, resection of the ulcer (the procedure of choice in those days) and even posterior gastroenterostomy were impossible. Therefore, an anterior gastroenterostomy was done. After a stormy convalescence the patient recovered and remained symptom-free for at least 15 years when he was lost sight of. The second case was that of a male in his late forties, showing roentgen evidence of a niche about 3 cm. in diameter with considerable indentation of the greater curvature. He was operated on by Dr. J. F. Erdmann. A local excision with posterior gastroenterostomy was done. Pathological report was ulcer, benign. The patient had many years of comfort postoperatively.

Since that time we have seen, and other observers have reported, numerous cases with niches varying from 6 to 10 cm. in which thorough pathological studies failed to reveal any evidence of malignancy.

Many of these ulcers of more than 2.5 cm. may heal after medical treatment. However, there may be recurrences, but this is still not sufficient evidence that the ulcer is cancerous. It must be emphasized that when there is a niche particularly on the lesser curvature, because of the excavation of an ulcer area and weakening of the adjacent wall, increased intragastric pressure by the filled stomach will cause a ballooning out of this area with protrusion. In such instances, on one examination the effect of intragastric pressure causes the niche to appear on roentgenogram. When the stomach is only partially filled some hours later, the niche has disappeared. Within a short time, when the ulcer is in the process of healing, the increased intragastric pressure no longer produces the niche effect. This explains why many cases are reported in which a niche has disappeared rapidly, and within a week or two the patient has a gastric hemorrhage.

On the other hand, there is another form of niche due to an ulcer on the lesser curvature which penetrates beyond the wall and becomes adherent to surrounding structures. In these cases, between the wall of the stomach and the niche there is a vacant space. The niche itself is often triangular rather than circular. Occasionally an air bubble may be seen on top of the niche. A niche of this type will be smaller when healing takes place, but some evidence of the niche remains even though the patient is symptom free. Held and Gray [11] suggested that the term *diverticulum* was more descriptive than the term niche. They spoke of two types: one that did not penetrate beyond the wall of the stomach was termed "pulsion diverticulum," and the penetrating type with adhesions to the surrounding structures was called "pulsion-traction diverticulum." Rehfuss [12] is in concurrence with this concept.

Conversely, a small sized niche less than 2.5 cm., on the basis of ulcer, may be the site of cancer formation. This has been recently reëmphasized

by Eusterman.[13] We recall a 43 year old male, with only a three to four year history of ulcer symptoms, who because of frequent recurrence of symptoms and inability to carry out medical treatment, asked for operative intervention. An ulcer of very small size on the lesser curvature was excised. The pathologist reported benign ulcer. The patient felt well for one and a half years, then began to suffer a recurrence of symptoms, presenting himself with an immense palpable mass in the epigastrium and a large liver. He was again operated on, and an inoperable carcinoma was found. In retrospect, we now feel that at the time of the first operation, there were already some cancerous changes in the ulcer which were not correctly evaluated by the pathologist, or that the early niche was primarily due to cancer.

What should be the criteria in determining whether an ulcer has become cancerous? It seems to us that the most stress should be placed on the greater persistence and aggravation of symptoms. Pain becomes worse and is not relieved by the intake of food, appetite diminishes, and there is gradual loss of weight. In these cases, above all, gastroscopy with biopsy must be done.

In the prepyloric region, if an ulcer becomes cancerous, we must rely on the clinical and gastroscopic evidence. Roentgen-ray examination may be extremely disappointing. If the patient has been previously examined by roentgen-rays, and some time later shows irregularity of the pylorus and progressive delay in the emptying, we have reason enough to resort to exploratory laparotomy. Clinically, vomiting is present despite the fact that stenosis is not complete. Fluoroscopic examination may show marked diminution in the peristalsis in the pyloric region and compensatory hyperperistalsis in the pars media. There is never the characteristic atony of benign stenosis. In the presence of the above findings, despite negative gastroscopic examination, surgical intervention is absolutely indicated.

The following case is cited here because it illustrates two important points: first, that carcinoma of the stomach can occur on an ulcer basis; second, that such a cancer, when resected, can give lasting local results without any local recurrence. The case is that of a male in the mid-fifties, who had suffered periodically from ulcer symptoms for 25 years. He suddenly began to have persistent pain and moderate loss of weight, but no definite roentgenologic evidence of cancer was demonstrable, except for slight deformity of the pylorus. No mass was palpable. He was operated on by Dr. Leon Ginzburg (at the Mount Sinai Hospital), who did a resection for pyloric cancer. The patient made an uneventful recovery, and felt perfectly well for about two years, when he again developed abdominal symptoms. This time a palpable mass in the mid-abdomen was felt. It was looked upon as a recurrence. Dr. Ginzburg * reoperated and found the cancer in the transverse colon. Dr. Paul Klemperer, pathologist at Mount Sinai, re-

* This was reported to us by Dr. Ginzburg, with whose consent we mention it here, since we did not see the patient at the time of recurrence of symptoms.

ported that the growth was an independent cancer, completely unrelated to the cancer previously found in the stomach. The cancer of the transverse colon was resected, and the patient again made an uneventful recovery.

There is a large group of cases in which the patient has ulcer symptoms, the underlying lesion, however, starting as cancer. Such cases simulate ulcer in that they have hunger pains and are relieved by the intake of food. However, there is a lack of periodicity, and unlike ulcer in which psychic trauma aggravates the symptoms, here dietetic errors play the major rôle. These errors lead to an increasing exclusion of many articles of food. The patient attributes the loss of weight to lack of food, but the loss of weight is even out of proportion to the diminished food intake. Sooner or later the appetite becomes capricious. These patients usually develop symptoms in the late forties or fifties. In most of them the roentgenologic examination may be entirely negative. Even careful mucous membrane studies may be uninformative. In order not to overlook the lesion, frequent gastroscopic examinations should be made, and even a suspicious finding is sufficient indication for operation. It is in these cases that valuable time may be lost in waiting for palpable or roentgenologic evidence.

Anemia. Since many of the cases of gastric cancer are accompanied by a marked anemia it would be well to analyze the anemia more carefully. Two types occur, a hyperchromic and a hypochromic anemia. It is very important to differentiate between these two clinically, because the therapy to combat each type is different.

The hyperchromic type of anemia co-existing with achylia in a case of carcinoma simulates the picture of pernicious anemia. The diagnosis of carcinoma having been established, it is necessary to introduce liver therapy besides blood transfusions and iron.

The hypochromic type of anemia should respond to blood transfusions and iron. In rare instances, the presence of a high degree of anemia may lead one to suspect actual bone marrow involvement due to metastases. Although bone metastases in cancer of the stomach are uncommon, some observers have reported an incidence as high as 5 per cent. All efforts should be made to diagnose the presence of bone metastases. Increased blood phosphatase and prolonged sedimentation time are sometimes found with bone metastases. Roentgen examination, particularly of the pelvis, spine and skull, should be done.

Farrow and Woodward have suggested that these patients should have four to five injections of testosterone propionate; if the concentration of calcium in the serum and its excretion in the urine are markedly increased bone metastasis should be suspected. In two cases, similar changes followed injections of estrone.

Finally, the study of bone marrow for the presence of cancer cells should not be neglected.

Conclusion

1. Despite all efforts at early diagnosis of cancer of the stomach, a large percentage of such cases are inoperable because of the extreme malignancy and rapid metastases.

2. Some cases are inoperable because the lesion exists in a silent area of the stomach and is asymptomatic until advanced beyond operability.

3. The percentage of cases (30 to 40 per cent) in which operability and even permanent cure is possible is of great practical importance. In these cases early diagnosis is most essential. Recent experiences have shown that gastroscopic examination has materially increased the percentage of early diagnosis of cancer.

4. We must bear in mind that cases of cancer which develop on a previously diseased mucous membrane as in case of gastritis, polyposis, gastric ulcer, have a tendency to grow much slower, are more benign in character and when diagnosed early, offer the patient a great chance for prolongation of life and even permanent cure.

5. Individuals with ulcer symptoms, without ulcer signs, should be looked upon with greater suspicion and more watchfulness for early cancer than those in whom ulcer is clinically and roentgenologically demonstrable.

6. The high degree of anemia and the size of the palpable mass should not deter one from operative intervention provided preoperative and postoperative treatment are carried out with the greatest care.

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THE LEAVEN OF PSYCHOSOMATIC MEDICINE*

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THE accomplishments of psychosomatic medicine are noteworthy; its objective is magnificent, but the name is unfortunate. Its comparatively recent usage makes it sound like the announcement of a marriage between body and mind, with the subdivisions and specialties of medicine and psychiatry in the bridal party. If the union of body and mind has just been consummated, then psychiatry for some time has sanctioned an illicit relationship. Long before the word psychosomatic was compounded, psychiatry had insistently taught that man was a total and indivisible unit and, therefore, in health and disease, every somatic process at once reverberated in all of the man and notably in his emotions; conversely that every emotional reaction, whether it was violent and pathological, like rage, or merely a feeling tone, like a mild state of satisfaction, immediately had repercussions in every tissue and cell of the body.

The basic idea of psychosomatic medicine is very ancient. More than 2500 years ago, the wise Socrates, returning from the Thracian campaign, reported that the Thracians realized that the body could not be cured without the mind. "This," he said, "is the reason why the cure of many diseases is unknown to the physicians of Hellas, because they are ignorant of the whole."

Nor was the appreciation of the entwining of the body and mind confined to the elect. From time immemorial it has been reflected in the language of the people: "I felt a lump in my throat"; "My heart jumped"; "My stomach dropped"; "I felt as though I had been pulled through a wringer"; etc.

Our allies, the Chinese, no doubt stimulated by frequent food scarcities, have elevated the stomach to a sentimental plane. Two lovers separated from each other might write in this vein: "My stomach is hungry for you." So, too, is there a psychosomatic note in this ancient and beautiful Chinese wish: "May Joy sing in the topmost boughs of your heart."

The dough of psychosomatic medicine was ready for a long time, but it needed the yeast of concrete evidence. This was supplied by the focusing of attention upon a group of clinical situations in which functional and structural met; or more accurately, a long path of functional symptoms, perhaps gastrointestinal, due to the anxiety of emotional conflict, came to the end of the trail in the structural pathology of a peptic ulcer. The yeast now became activated and the leavening began.

Evidence was offered from every department of medicine and its specialties. One treatise alone listed 2251 references in this order of observed

* Presented at the meeting of the American College of Physicians, St. Paul, Minnesota, April 20, 1942.

frequency: cardiovascular, genitourinary, gastrointestinal, general metabolism, endocrine, respiratory, dermatological, special senses, nervous system, musculature, osseous system.

In internal medicine and its various divisions how effective in terms of treatment will be the psychosomatic leavening? Presumably internists, cardiologists, genitourinary specialists, gastroenterologists, endocrinologists, dermatologists, laryngologists and others will continue to treat patients whose functional symptoms fall into the groups in the treatment of which they are skilled. This is right and proper. Those specialists who understand the real implications of "functional" will continue to treat patients successfully. However, there are others who are not so well informed.

The gastroenterologist, the genitourinary specialist, the dermatologist and others have armamentaria, instrumental and pharmacological, useful in the treatment not only of organic but of functional symptoms. There is nothing in the determinations of psychosomatic medicine which would frown upon the employment of specialized technics and drugs. Even psychiatrists prescribe drugs, massage, hydrotherapy, heliotherapy and many other measures. Functional symptoms involve the revolution of a vicious somatopsychic circle—emotional, functional derangements of organs expressive of the emotional conflict, more emotional reaction, more functional incapacity and so on, until the human machine runs down or, perhaps, gives out, and there remains the scar of structural pathology. Often, it is legitimate to attempt to interrupt the revolution of the vicious circle in any of its segments and sometimes well conceived and directed physical and drug therapies are followed by considerable improvement.

There are certain conditions under which concrete therapies are not helpful, and indeed are harmful, serving only to impress more deeply the functional symptoms which are present or others which may take their place.

These conditions are as follows:

1. If the patient is not given clearly to understand that these various special therapies and drugs, although they may be symptomatically helpful, may lessen somatic distress and promote general improvement, yet of themselves cannot bring about adjustment or recovery.

2. This situation becomes particularly dangerous if the patient comes to believe that the symptoms are actually due to some insignificant or conjectural defect—a minor deviation, a dead tooth, a trifling ptosis of the stomach. Once patients believe these things firmly, then the impress of the functional symptom-complex becomes indelible and hope of recovery passes.

3. The most important condition is the failure to recognize underlying fundamental psychopathology and to utilize the understanding acquired in the basic treatment of the functional symptoms. If this is not done, it is as grievous an error as would be the failure to remove a beginning malignancy of the breast. Failure to do this could not be compensated for by any amount of expert care, vitamin therapy and special treatments. Neither

can any amount of instrumentation, gall-bladder drainages, vaccines, endocrine therapy, etc., bring about a favorable result unless the determining underlying emotional conflict is resolved.

Perhaps, these three actual and very usual situations will be illustrative.

Case Reports

Case 1. A man 49 years old, with a wife 35 and two healthy children, described himself as desperate because he was sexually impotent. Pathetically he told of treatments to regain potency and happiness: genitourinary instrumentation, general and prostatic massage, hydrotherapy, electrotherapy, heliotherapy, a sheaf of prescriptions for endocrine products, faithfully taken. His impotence was no better. Indeed, to it had been added annoying sensations and sharp pains in the perineum, burning on urination, nocturnal emissions, headaches, insomnia, loss of energy and concentration, etc.

Case 2. A married woman, aged 42, complained of severe nausea, "sick stomach," vomiting, anorexia, headache, backache, vertigo, etc. She had had two rest cures, numerous gastrointestinal roentgenograms, special corsets for gastroptosis, and now she was having weekly gall-bladder drainages.

Case 3. A 22-year-old student wanted to leave college since he felt he was too sick to go on and as he said: "I would rather quit than flunk. It's no use trying. I can't concentrate."

Tuberculosis had been suspected. He was being given nose and throat treatments twice weekly. He had had many dietary and rest treatments, efforts to increase his weight.

At the very first interview in each instance, the following facts were elicited. They had never been brought to the surface before.

Case 1. The man with the impotence had been dominated far into manhood by a positive, aggressive mother. He was 14 years older than his wife whose sex needs were strong. His symptoms appeared after an unsuccessful attempt at sexual intercourse. He thought his wife was irritated and impatient at his failure.

Case 2. The woman with the gastrointestinal symptoms had lost sexual desire. Sexual relations had become unpleasant and painful. By various subterfuges she had decreased the frequency of the sex act, but was filled with anxiety, lest her husband should tire of her and leave her.

Case 3. The young student was enormously relieved at being given the opportunity of relieving his mind, deeply troubled and remorseful, because of masturbation. During much of his life he had been tied too tightly to the apron strings of an emotionally possessive mother. She had warned him excessively about "girls." The masturbation had not been continuous from childhood but had been resumed soon after entering college, upon the heels of three heterosexual experiences, occurring in a setting conducive to embarrassment, feelings of inferiority and fear of discovery.

Three clinical situations have been briefly and crudely sketched. On the one hand, there were genitourinary examinations, gastrointestinal and gall-bladder tests, studies of the nose, throat and sinuses, and roentgenograms of the chest; on the other hand, a surface revealing of three emotional conflicts. The first, the physical, dictated a variety of physical therapy, urethral instrumentation, prostatic massage, general massage, hydrotherapy, endocrine medication, the wearing of special corsets, gall-bladder drainage,

nose and throat treatments, rests and diets; the second, the emotional, led to a moderate amount of psychotherapy, to the opportunity to talk over troubles that were not physical, to explanation of underlying mechanisms and a frank facing of their implications, to correction of faulty mental attitudes, and to slight adjustments in the environment.

If the obvious lessons which these clinical situations and thousands of similar ones teach are not learned and learned well by all of us, then the yeast of psychosomatic medicine will fail to leaven the dough of practice, and there will be only a half-baked loaf which would fall far short of rising to the promised and anticipated level of medical progress.

Under the protection of my brother Fellows of the American College of Physicians, I am emboldened to hint that surgeons might well profit from the lessons of psychosomatic medicine. The scalpel of the surgeon, no matter how skillfully wielded, often cannot avoid cutting through protective psychological tissues. By this, I mean that every human being has one and usually more flaws in his or her psychological armor. However, the majority of us meet life adequately enough in spite of our flaws. Nevertheless if, when the psychological resistance is lowered, an opportunity presents, then the flaw will be enlarged, the area of vulnerability increased and functional protective symptoms will appear as an escape mechanism. Often a surgical operation is such an opportunity. Whenever possible, there should be a psychological survey before an operation; adequate psychological preparation for anesthesia and postoperative treatment which is not only surgical but also psychological. Attention to these few measures based on the principles of psychosomatic medicine would prevent a deal of chronic functional invalidism.

The way to get something done thoroughly is to begin at the beginning. The beginning is in the preclinical years of medical education. Medicine not only has its physics or somatics but also its "psychics" or psychogenetics. There could be a true and helpful teaching parallel. If there are livers and spleens and hearts in anatomy, so, too, is there an anatomy of psychology which should study normal emotions, consciousness, memory, etc. If there is a physiology which teaches how organs work, so too, and at the same time, should a physiology of mental functions be taught. The student should learn how they work. Paralleling histology, the microscopic study of normal organs and tissues, there should be given opportunities to become familiar with the finer subdivisions of mental functions; for instance, remote and recent memory, the gradations of normal consciousness, the infinite variety of emotional shadings. When the Department of Pathology is demonstrating gross morbid lesions, luetic aortitis, liver abscess and what not, the Department of Psychiatry should be showing the gross pathology of the mind, marked emotional deviations like profound melancholia or complete dementia. Likewise should there be the twin teaching of microscopic pathology, let us say, on the one hand, the study of a cross-section of an arteriosclerotic vessel or the walls of an abscess, on the other a span of

amnesia or the degrees of katatonic stupor. If the loaf of medical practice is to be thoroughly leavened, the medical student must be given from his first week in medical school the opportunity of studying all of the man and not only a hypothetical somatic half.

We are in the midst of the greatest World War that has ever cursed humanity. As it happens, among other things modern war constitutes a huge laboratory of psychosomatic medicine. Statistics from World War No. 1 indicate that one-seventh of all war casualties were neuropsychiatric and, excluding wounds, the proportion was one-third. The Veterans' Bureau has already expended more than one billion dollars for the care of neuropsychiatric disabilities incurred in World War No. 1. I think I may predict with safety that the neuropsychiatric problem eventuating from this war will be much greater than from the previous one.

As you know, these casualties will be largely psychoneurotic. They will consist of "shell shock" (conversion hysteria), neurasthenia, anxiety neuroses, and a relatively smaller number of psychoses. In other words, a very large majority of the casualties will consist of functional symptoms, that is, there will be demonstrated again on a massive scale the close entwining of body and mind and there will be clinical examples that properly fall within the domain of psychosomatic medicine.

Reports would already indicate that a very large number of functional symptoms are within the gastrointestinal field. Furthermore, there have been definite indications that sometimes anxiety is productive of structural pathology, perhaps chiefly peptic ulcer.

It is important to note that there has been a definite difference in the Army and in civilian life. I think there will be no change in the number of neuropsychiatric casualties in the armed forces. As a result of bombing in England, in London, Liverpool, Coventry, Plymouth and other places, it appears that functional symptoms in civilians are quite rare and constitute less than 2 per cent of the hospital admissions. Here we have an important fact which needs thorough consideration by the students of psychosomatic medicine. Evidently, even though the stress and strain are great, if the human being is not away from his home and from those whom he loves and who love him, he does not succumb to "shell shock." This means that he retains a protective measure of security.

In closing, may I say that in this great war crisis which is being fought on so many fronts we need another Socrates. Indeed, we need more than one. If we can have them, I predict that they will return after the war is over and tell us in much the same words that Socrates told the Greeks after he returned from the second Thracian campaign: "It is important, extremely important, never to forget the close relationship between the body and the emotions and it is important to remember that the body cannot be cured without close attention to the mind."

SEVERE INJURY TO KIDNEYS AND BRAIN FOLLOWING SULFATHIAZOLE ADMINISTRATION: HIGH SERUM SODIUM AND CHLORIDE LEVELS AND PERSISTENT CEREBRAL DAMAGE *

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FIVE patients with a history of recent sulfonamide medication have developed an unusual type of renal insufficiency, as well as evidence of injury to the brain. The patients presented a temporary, severe disturbance of serum sodium and chloride concentration, which was responsible, at least in part, for the death of two patients. In all cases there were signs of injury to the central nervous system, which persisted in two patients despite return of the blood chemistry to normal.

Case 1. This 25 year old colored laborer was brought to the hospital because of vomiting and delirium. His past health had been good. Ten days before admission he complained of fever, cough, and pain in the chest. Three days later his physician found signs of pneumonia and prescribed sulfathiazole, 3 grams per day for two days and then 1.5 grams per day for four more days. On the second day of treatment, the patient began to vomit. After three days of sulfathiazole therapy, he retained no food or fluids and passed little or no urine. He became drowsy, confused, and finally delirious.

On admission to the hospital, a week after the first dosage of sulfathiazole, the patient was stuporous and confused. Temperature was 98.6° F., pulse 90, respiration 25 and blood pressure 130 mm. Hg systolic, 100 mm. diastolic. Skin and mucous membranes were dry and icteric. An uremic frost was observed on the skin. There were râles and impaired resonance over the right lower lobe of the lung. Heart appeared normal. Abdomen was distended. There was slight tenderness in the flanks. The right kidney was just palpable. Reflexes were sluggish. Chvostek's sign of tetany was present.

A summary of the blood studies appears in table 1. It will be noted that there was initial hemoconcentration. Polymorphonuclear leukocytosis was present on every examination, rising as high as 37,000 without any evidence of infection. On admission, there was azotemia with acidosis and reduction of serum chloride concentration. Serum phosphorus was 16 mg. per cent. Urine was scanty and contained protein (3+), small amounts of bile and urobilin, and a great deal of amorphous debris in which red and white blood cells and large hyaline casts could be seen. No sulfonamide crystals were observed. Roentgenographic examination of the lungs revealed no consolidation.

The patient received 5000 c.c. of fluids intravenously on the first three days. With a hypotonic glucose-saline mixture and small amounts of sodium lactate, the dehydration and acidosis were relieved. From the fourth day onward the fluid intake was maintained at an average of 3700 c.c. per day, with a total daily sodium chloride

* Received for publication March 13, 1943.
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TABLE I

Summary of Blood Analyses in Case 1

Days After Sulfonamide	Hematocrit %	W.B.C. thousand	Blood N.P.N. mg. %	Serum Cl. m.eq./l.	Serum CO_2 Comb. Power Vols. %	Blood Sulfonamide mg. %		Serum Protein gm. %	Icterus Index
						Free	Total		
7	51	13	320	84	27	4.6	9.2		50
8	41	20	296	86	37				40
9	49		307	84	42			6.5	40
10	43		280	88	49	3.8	8.2		25
11	41	37	304	87	42				25
12	39	31	310		47				20
14	33	30	304	97	43				10
15	25		290					5.8	10
16	25	30	270	116	49	0.8	1.8		
17			256						
18	26	20	192	132	45				
21	22	13	132		44			6.7	
23	20	9	110	146	44	0	0		

intake of 9 grams. The urine output slowly increased from 300 c.c. on the first day to 1000 c.c. on the fifth day.

For the first week in the hospital, the patient improved very slightly. Heart rate was very rapid. Digitalis was given, but was discontinued when auriculo-ventricular nodal tachycardia developed. There was bleeding tendency with progressive anemia (hematocrit 33 per cent after one week). The serum chloride was still subnormal.

At the end of one week in the hospital, a large volume of urine was being excreted but accurate measurement was impossible because of incontinence. Blood analyses showed a progressive decrease in the nonprotein nitrogen from this point onward. Serum phosphorus fell to normal, and sulfathiazole disappeared from the blood. The urine remained grossly bloody, and the hematocrit fell steadily despite the appearance of dehydration.

At the same time, the serum chloride concentration began to increase. Salt intake was reduced and then eliminated without any obvious effect on the constantly rising serum chloride. The fluid intake averaged 3800 c.c. per day. The urine chloride was only 30 m.eq./l. even when the serum chloride was at its peak.

As the uremia subsided, the patient responded to stimuli and appeared to know what was going on about him. He was unable to speak despite obvious efforts. Movements were purposeful but poorly coördinated. On the last two days of life, when the serum sodium and chloride rose to extreme heights, the patient became stuporous again. He appeared progressively more dehydrated despite the large fluid intake. Breathing was deep and somewhat faster than normal. It became obvious that oral fluids would not suffice to halt the constantly rising salt concentration of the blood. The intravenous administration of 300 c.c. of salt-free 5 per cent glucose solution was followed by pulmonary edema, which subsided only to return some hours later, terminating in the death of the patient. On the last day of life (sixteenth day in the hospital), serum sodium was 181.5 m.eq./l., potassium 5.2 m.eq./l., chlorides 146.0 m.eq./l., and carbon dioxide combining power 43.8 vols. per cent. Blood nonprotein nitrogen was 110 mg. per cent, urea nitrogen 95 mg. per cent and sulfathiazole not present in detectable amounts.

Autopsy. Anatomical Diagnosis: Many focal lesions in renal cortex (obstruction of tubules in cortical rays and of intercalated segments of distal convoluted tubules by hyaline and calcified casts; small foci of interstitial scarring and atrophied

proximal convoluted tubules); changes in widely scattered epithelial cells in glomeruli and tubules of cortex and pyramids (necrosis, calcification and regeneration); scattered thick hyaline foci in arterioles, glomerular capillaries and basement membranes of glomeruli and tubules; organizing thrombi in interlobular renal veins and in a few tiny veins in glomerular layer of adrenal cortex; rupture of tubules into interlobular veins; proliferating epithelium in thrombi; few small hemorrhages, and edema of many cells, fascicular layer of adrenal cortex; history of moderate hypertension; hypoplasia of bone marrow; marked anemia (history); atrophy of central liver cells; jaundice; foci of edema and gliosis in brain; many minute pulmonary hemorrhages, purulent bronchiolitis, lobular pneumonia, and pulmonary edema; slight edema of ankles; atrophy of germinal epithelium, hyperplasia of Sertoli cells and scars in interstitial tissue of testes; metaplasia of epithelium of small pancreatic ducts and dilatation of acini; ulcers over sacrum.

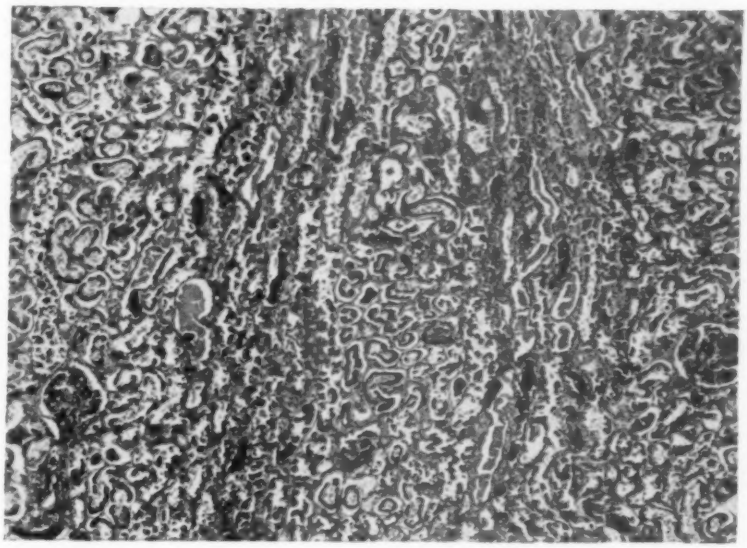

FIG. 1. (Case 1). Calcified and hyaline casts within certain tubules of the cortical rays.

Kidneys: No gross lesions were recognized. Microscopic sections showed long segments of many tubules in each cortical ray to be obstructed and some of them moderately dilated by casts. Some of the casts were hyaline, like coagulated protein. Some casts contained necrotic epithelium and a few leukocytes and many were calcified. A few of the calcified casts lay against the basement membranes of tubules and were covered by a thin layer of regenerated epithelium. A few others appeared to lie partly outside the tubules, in the interstitial tissues. Some of the affected tubules were collecting tubules and more were spiral segments of proximal convoluted tubules.

Besides the obstructed tubules in the cortical rays, there were many other small foci of irregular outline in the renal cortex where tubules were moderately atrophied and separated from each other by loose scar tissue. Still other convoluted tubules contained a few necrotic epithelial cells, and against the basement membranes of some a few cells full of "colloid" drops and a few in mitosis were found. Calcified or hyaline material was present in the intercalated segment of most distal convoluted tubules.

The glomeruli, examined under the oil immersion lens, all showed changes in some of the cells of the visceral and parietal epithelium. There were a few necrotic cells and a few contained "colloid" droplets.

Segments of the basement membranes of many tubules, of Bowman's capsules, and of the glomerular capillaries were irregularly thickened and hyaline, and there were similar small foci in the muscularis of a few arterioles near the glomeruli. In some of Bowman's spaces and between some glomerular capillaries were small collections of hyaline material resembling serum protein. Red blood cells were found in a rare cortical tubule.

In the collecting tubules of the papillae and to a less marked degree in tubules of the boundary zone of the medulla (convoluted and Henle's tubules) there was evidence of damage to the epithelium. A good many scattered cells were necrotic and lay either against the basement membrane or in the tubules. There was considerable new epithelium. Some of the cells were very thin and basophilic and there were numerous mitotic figures.

Deep in the cortex and in the boundary zone, a good many of the interlobular veins were filled with organizing thrombi. Some of these veins communicated with ruptured tubules, and the thrombi contained proliferating tubular epithelium.

Case 2. This 54 year old, colored housewife was brought to the hospital in coma. The patient had been in good general health except for rather frequent attacks of indigestion and abdominal pain. Five days before admission, she complained of generalized aching and fever. On the next day, her physician noted signs of bronchitis and prescribed sulfathiazole in five doses of one-half gram. When the patient failed to improve, sulfapyridine was given for five doses of one-half gram. The temperature fell to normal, but the patient began to vomit and passed little or no urine in the two days before admission.

On admission to the hospital, the patient was described as an obese woman in deep stupor. Temperature was 101.6° F., pulse 140, respirations 28, and blood pressure 62 mm. Hg systolic, 40 diastolic. Skin and mucous membranes were deeply icteric and very dry. Breath was uremic. Respirations were deep and labored. The lungs appeared normal. Heart was normal in size and quality of sounds, but there were frequent extrasystoles, sometimes occurring in rapid bursts. There was no tenderness in the flanks, but the patient resisted deep palpation of the right upper quadrant of the abdomen. Tendon reflexes were hyperactive.

There was slight anemia and a leukocytosis of 14,600 with 83 per cent granulocytes. Icteric index was 100. A small amount of murky, brown urine was obtained. This gave strong tests for protein and bile and contained many white and red blood cells with a great variety of casts. No sulfonamide crystals were identified. A summary of the blood analyses is presented in table 2. Serological tests for syphilis were positive.

Although there was much to suggest obstruction of the common bile duct, the surgical consultant felt that because of the patient's precarious condition immediate operation was not justified. On the fourth hospital day, the patient was deeply jaundiced and bleeding from the mucous membranes despite transfusions and vitamin K, but subsequently the jaundice diminished and finally disappeared.

On the first day in the hospital, the patient was given plasma and fluids (hypotonic saline-lactate-glucose mixture) totaling 5 liters. During the subsequent week, the average daily intake was 4.8 liters of fluid with 11 grams of salt. The serum chloride concentration remained subnormal. The urine output on the first three hospital days was 40, 100, and 200 c.c., but during the next week it increased steadily.

At the end of one week in the hospital, the patient began to take some notice of the environment and tried to follow simple commands. Physical status was definitely improved. During the next 11 days, the patient was able to take a liquid diet, and

TABLE II

Summary of Blood Analyses in Case 2

Days After Sulfonamide	Hematocrit %	W.B.C. thousand	Blood N.P.N. mg. %	Serum Cl. m.eq./l.	Serum CO_2 Comb. Power Vols. %	Blood Sulfonamide mg. %		Serum Proteins gm. %	Serum Bilirubin mg. %
						Free	Total		
5	44	15	120	98	28	1.6			
6	32	15	136	95	42	1.4			9.5
7	34	10	132	89	37	1.2	2.1	4.8	10.0
8	34	21	172	92	48				
9	33	27	184	95	41				11.0
12	33	36	208	98	46	1.2	1.9	6.0	5.3
14	31	24	176	105	50	0.8	1.5	6.0	3.1
17	29		124			0.4	1.4		2.7
19	26	12	112						2.1
22			160	160*	43			8.8	1.6
23	33	9	128	139†	44			7.5	
26			88	126	46	0	0		2.2
30			62	116	44				
33			40	110	50			6.4	1.0
40	27		34	105	58				0.9

* Estimated serum sodium 195 m.eq./l., total base 210 m.eq./l.
† Observed serum sodium 174.6 m.eq./l., potassium 5.1 m.eq./l., calcium 4.8 m.eq./l. Observed total base minus magnesium 185.5 m.eq./l

parenteral therapy was discontinued. The average daily fluid intake was 2500 c.c., with 2 grams of salt, comparable to a "salt-free" régime. Urine output was profuse, but could not be measured because of incontinence. The blood nonprotein nitrogen decreased steadily. The physical condition remained the same save for slight, progressive dehydration until the seventeenth hospital day, when the patient began to have some hyperpnea and lapsed into a deep stupor. On the eighteenth hospital day, the blood chemistry revealed an enormous rise in serum chloride concentration to 160 m.eq./l. without appreciable reduction of the carbon dioxide combining power, indicating a great increase in serum sodium. Salt-free glucose solution was given intravenously without ill effect. On the next day, serum chloride concentration was 139 m.eq./l, serum bicarbonate 18.7 m.eq./l., serum proteinate 18 m.eq./l. (7.5 gm. per cent) and serum phosphate 4.5 m.eq./l. (6.7 mg. per cent), indicating a determined acid concentration of 180 m.eq./l.; serum sodium was 174.6 m.eq./l., potassium 5.1 m.eq./l., and calcium 4.8 m.eq./l. (9.5 mg. per cent), indicating a total base minus magnesium of 185.5 m.eq./l. It is evident that the primary disturbance was a great increase in the serum sodium and chloride concentration. The urine chloride concentration on this day was only 25 m.eq./l., showing a total lack of response to the need for chloride excretion.

During the next two weeks, the patient was given salt-free glucose solution intravenously to make a daily total fluid intake of three liters a day. On this régime, the serum chloride concentration slowly fell, reaching normal (105 m.eq./l.) on the thirty-sixth hospital day. On the same day the blood nonprotein nitrogen was 34 mg. per cent. With a liberal fluid intake and a "salt-free" diet, no further chemical disturbances were encountered.

The patient never regained a normal state of consciousness. After the recovery from uremia and hyperchloremia, she was aware of people and appeared to respond suitably to stimuli. She never spoke coherently and movements were jerky and poorly performed.

A constant temperature elevation to 101° F. appeared on the fourth week in the hospital. During the fifth week, fever rose to 102° F. and remained at this level until death, seldom fluctuating more than a degree in either direction. The patient was intractibly distended, but complained of no localized abdominal pain or tenderness. Jaundice did not return. *E. coli,* proteus and an alpha-hemolytic streptococcus were grown from the blood at various times. Administration of a single dose of sulfathiazole was twice followed by a chill and high fever. Sulfadiazine was given without any obvious effect. The patient became gradually weaker and died on the sixty-fourth day in the hospital, 10 weeks after the onset of her illness, seven weeks after the height of the electrolyte changes, and a month after return of the blood sodium, chloride and nonprotein nitrogen to normal.

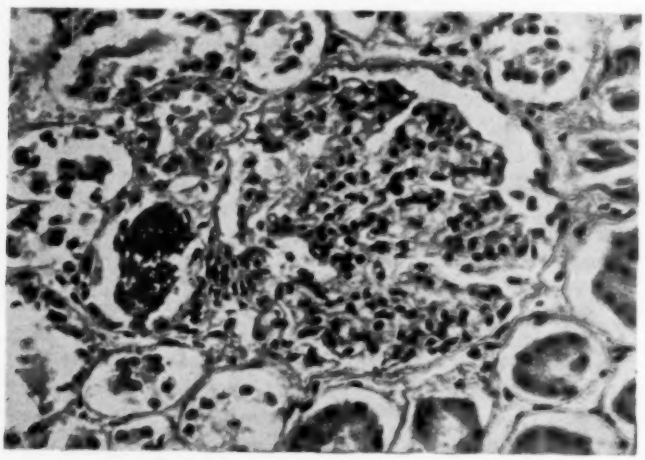

FIG. 2. (Case 2). A calcified cast in the intercalated segment of a distal convoluted tubule.

Autopsy. Anatomical Diagnosis: Few small focal lesions in cortex and medulla of kidneys (obstruction and dilatation of tubules, and interstitial scars); foci of edema and gliosis in brain; calcification of small arteries and old infarcts in corpora striata; cholelithiasis and chronic cholecystitis; fractured gall stone in common duct; sinus tract between gall-bladder and abscess in scar tissue about neck of gall-bladder; multilocular abscesses in liver; rupture of abscess, left lobe of liver; serofibrinous peritonitis; partial intestinal obstruction (fibrous adhesions binding loops of ileum); chronic ulcers in ileum proximal to adhesions; otitis media; decubitus ulcers, back, heels, knees; abscesses in muscles of thighs; calcified and caseous tubercles in left bronchial lymph node, extending into left lung; serofibrinous pleurisy; disseminated soft tubercles in spleen, liver, bone marrow, adrenals, and lymph nodes; capillary thrombi and hemorrhages in endometrium; slight hyperplasia of bone marrow; small focus of pulmonary fibrosis, left; fatty liver; slight chronic cystitis; myomata uteri; fibrous pericardial adhesions; moderate arteriosclerosis of aorta.

Kidneys: No gross lesions were seen. Sections were made from 16 blocks of tissue. In all of them there were a few tubules in every corticle ray and in the boundary zone of the medulla of every pyramid filled with hyaline material. A rare tubule contained a calcified cast. The obstructed tubules in the boundary zones had the location and size of descending loops of Henle. In the cortical rays some of the affected tubules could be recognized as ascending loops of Henle, and in the cortical labyrinths there were casts in some of the intercalated segments of the distal convoluted tubules. In the cortex of the kidneys there were a few small scattered foci

composed of several moderately atrophied tubules separated by fairly cellular new-looking scar tissue.

Case 3. This 19 year old white housewife was admitted because of high fever, stupor and anuria. She had been in good health with no evidence of preëxisting nephritis. Two weeks before admission, when the patient had passed uneventfully through her first pregnancy, labor was induced. Labor was prolonged and several vaginal examinations were said to have been made without adequate sterile technic. Because of some fever the patient was given sulfathiazole 6 grams per day for four days post-partum. The patient improved slowly after a difficult delivery, and the temperature returned to normal. Because of nausea and occasional vomiting, sulfathiazole administration was stopped on the fourth day post-partum. On the seventh and eighth days, there was intermittent fever of 101° F. with very questionable evidence of pelvic infection and no other obvious source of fever. Sulfathiazole was again given in doses of 7 grams on the ninth day and 3 grams on the next day. Temperature promptly rose to 105.4° F., pulse rose steadily to over 170 per minute and the blood pressure fell to 80 mm. Hg systolic, 40 mm. diastolic. The patient became deeply stuporous and unresponsive. Very little urine was passed for four days. Sulfathiazole was discontinued when no adequate evidence of infection was found. Fluids and blood were given by vein.

On the twelfth day post-partum, the patient was admitted to the medical ward. She was deeply stuporous. There were fever, tachycardia and dehydration. Muscles showed a coarse, jerky tremor. Chvostek's and Trousseau's signs of tetany were absent. Reflexes were hyperactive, Babinski's sign not present. The usual post-partum changes in breasts and uterus were noted.

The red blood cell count was 3.85 million and a white blood cell count was 14,000 with polymorphonuclear cell increase. Urine was dilute and contained protein (3+), many white blood cells and a few red blood cells. No crystals were seen. The blood nonprotein nitrogen was 100 mg. per cent; free sulfathiazole concentration was 8.8 mg. per cent, with a very high total drug level of 18.8 mg. per cent. Serum chloride was reduced to 89 m.eq./l. and the carbon dioxide combining power to 23 vols. per cent. Serological tests for syphilis were negative.

Because of dehydration and acidosis, the patient was given by vein 5000 c.c. of fluids containing 10 grams of salt as well as glucose, on the first day on the medical ward. The acidosis was improved following the administration of sodium lactate. Because of the development of hyperchloremia in the previous patients, this patient was then given only 4 grams of salt per day for the two subsequent days. Liberal amounts of fluid were given by vein, and the urine output increased to over 1000 c.c. per day. On this régime, the serum chloride remained below 90 m.eq./l. The salt intake was increased to 12 grams and 8 grams on the next two days, raising the serum chloride concentration to 106.4 m.eq./l. Blood nonprotein nitrogen fell rapidly to 44 mg. per cent.

The patient was then placed on a salt-poor régime (4 grams of salt with 4000 c.c. of fluid). In three days, the serum chloride concentration rose to 117.5 m.eq./l. The salt intake was reduced to approximately 2.5 grams per day (a "salt-free" régime). On the next day, the serum chloride rose to 124 m.eq./l. with the spinal fluid chloride concentration 161.2 m.eq./l. The blood nonprotein nitrogen was 56 mg. per cent. The slowly rising temperature reached 105° F.

The fluid intake was raised to 5000 c.c. per day, approximately half of this amount being given intravenously as 5 per cent glucose solution. The temperature fell and the serum chloride concentration gradually decreased to normal (105 m.eq.) during the next week. At this time, the serum carbon dioxide combining power was 53 volumes per cent and the blood nonprotein nitrogen was 26 mg. per cent.

During the development of hyperchloremia when the serum chlorides were 117.5 m.eq./l., the urine chloride concentration was 44 m.eq./l. and the total urine chloride output was 2.18 grams in 24 hours. Three days later, when the serum chloride concentration was 122.5 m.eq./l., the urine chloride concentration was 44.4 m.eq./l., and the total urine chloride output was 2.17 grams in 24 hours. During the fall in serum chloride concentration, there was only a slight increase in urine chloride concentration and scarcely any change in the daily output of chloride. Apparently, the large water intake first produced a dilution of the extracellular electrolytes rather than an increased chloride output. After several days, the patient reached a nice balance of intake and output.

When the serum chloride fell to 110 m.eq./l. and the fever disappeared, a mannitol clearance was performed.* At this time, the urine volume and chloride concentration were the same as during the height of the hyperchloremia. This test showed an average reduction of glomerular filtration to 30 per cent of the expected normal value. Parallel studies of serum and urine chlorides showed that 97 per cent of the chloride in this glomerular filtrate was reabsorbed while only 90 per cent of the water was reabsorbed. Phenolsulfonphthalein excretion was 45 per cent in two hours. On the next day, urea clearance was 29 c.c. per min. The nonprotein nitrogen was 34 mg. per cent.

As the uremia and hyperchloremia disappeared, the patient's responsiveness to the environment returned, but gross neurological defects became more obvious. It was noted that the patient failed to move the left arm and the right hand. The tongue and jaw also could not be moved normally. All of these parts showed a coarse, jerky tremor. In the legs, the tremor had diminished and voluntary movement was improving. The tremor was aggravated by attempts at movement. Swallowing of food was difficult. The patient smiled and wept on appropriate occasions.

During the next month, atrophy of the right thenar eminence and of muscles of the right leg became obvious. The electrical reaction of degeneration was demonstrated in the right opponens pollicis. The left fifth finger was held in full extension, whereas the other fingers were flexed. The left wrist was held in extension. Elsewhere, a steady return of function was evident. Muscles were atonic, movements were jerky, and reflexes were hypoactive, but gross movement of all four extremities was possible. Babinski's sign was absent.

Three months after the sulfathiazole administration, the patient had regained fair strength and control of most of her muscles, although tremor and poor coördination prevented any fine movements. For several weeks, she had made halting efforts to speak, and words were becoming clearer. With the return of speech, the patient confirmed the impression that no sensory loss had occurred. She remained very euphoric.

Case 4. This 63 year old white paper-hanger was admitted to the hospital because of epigastric pain and anemia. His health had been good until two months before admission, when he noted the gradual onset of deep, gnawing epigastric pain, unrelated to meals, but relieved by soda. One month later, the pain was worse and the stools became dark in color. The patient complained of spells of weakness and faintness.

The only abnormalities on examination were pallor and tachycardia. Blood pressure was 118 mm. Hg systolic, 68 diastolic. The red blood cell count was 1,800,000 without change in cell size or color. Stools were tarry and gave strongly positive chemical tests for blood. Urine had a specific gravity of 1.020 and contained no sugar or protein, occasional white blood cells, but no red blood cells or casts. Roentgenograms demonstrated a deep ulcer on the lesser curvature of the stomach.

* With the kind assistance of Dr. E. V. Newman.

The blood nonprotein nitrogen was 49 mg. per cent.* Serum chloride was 106.6 m.eq./l., carbon dioxide combining power 56 volumes per cent and protein 4.6 grams per cent.

The patient improved briefly and then suffered an exsanguinating hemorrhage, during which six liters of blood were necessary to keep the systolic blood pressure above 90 mm. of mercury. After two days without any cessation of bleeding, a subtotal gastrectomy and anterior Polya anastomosis were performed. Sulfathiazole powder was applied locally, and sodium sulfathiazole was given intravenously in four doses of 4 grams over a period of 48 hours. During these two days, the patient received 5500 c.c. of fluid by vein, of which approximately one-third was physiological sodium chloride solution. One hour after the last sulfathiazole injection, the blood sulfathiazole concentration was high (14.9 mg. per cent). At this time, the blood nonprotein nitrogen was 80 mg. per cent, serum chloride was 95.6 m.eq./l., carbon dioxide combining power was 74.8 volumes per cent, and plasma protein was 6.3 gm. per cent. Only 175 c.c. of urine were passed on the next day, but the blood nonprotein nitrogen did not rise and the free sulfathiazole level fell to 6.3 mg. per cent. Following this the urine volume gradually increased. The urine contained protein, a few red and white blood cells, many casts and numerous sulfathiazole crystals. The free sulfathiazole level fell to 1.8 mg. per cent on the next day but serum chloride concentration rose to 120 m.eq./l. The patient had been receiving 4 liters of parenteral fluid each day, containing 9 grams of sodium chloride (38 m.eq./l.). When the high serum chloride concentration was noted, salt intake was eliminated save for that contained in transfusions of blood. Despite the low sodium chloride intake and the liberal fluid intake, the serum chloride concentration on the next day was 142 m.eq./l. The carbon dioxide combining power was never below the normal level of 55 volumes per cent (bicarbonate 23.5 m.eq./l.). Blood nonprotein nitrogen remained between 80 and 90 mg. per cent. The urine output was profuse but could not be measured because of incontinence.

The patient's condition was most precarious during the hemorrhage, and he failed to rally after operation. With the hyperchloremia, he became irrational and stuporous, and his breathing was more labored. At the same time, evidence of localized peritonitis was noted and it appeared that a leak had developed about the gastroenterostomy. This was repaired, but the patient died on the next day (the eighth day in the hospital). Blood drawn 12 hours before death had a nonprotein nitrogen of 82 mg. per cent and serum chlorides 142 m.eq./l.

Autopsy. Anatomical Diagnosis: Chronic gastric ulcer (removed at operation): serofibrinopurulent peritonitis; marked anemia (history of massive hemorrhages); atrophy of central liver cells; minute hemorrhages in adrenals and islands of Langerhans; purulent bronchitis and slight lobular pneumonia; apical pleural scars; emphysema; moderate arteriosclerosis; history of sulfathiazole therapy, blood transfusions and renal insufficiency; marked dilatation of terminal collecting ducts in some renal papillae; obstruction and dilatation of few tubules in renal papillae, pyramids and cortex by casts (granular, hyaline and calcified material; red blood cells and hemoglobin).

Kidneys: No gross lesions were seen. Sections from 23 blocks were examined microscopically. There were a few minute areas of atrophied tubules and hyaline glomeruli, old lesions probably caused by intrarenal arteriosclerosis. There was no evidence of wide-spread damage to the renal epithelium.

In several papillae the large collecting tubules were greatly dilated, although no crystals or other obstructions remained in the stained preparations, and no crystals

* The influence of gastrointestinal bleeding in raising the blood nonprotein nitrogen concentration makes the interpretation of this determination difficult throughout this patient's course.

were seen in the gross specimen. Some of the terminal ducts, however, were dilated and filled with red blood cells and granules of hemoglobin.

In addition there were a few obstructed and slightly to moderately dilated tubules scattered higher in the papillae and medulla, and in the renal cortex. Some of these contained hyaline and granular material and a few contained calcified casts.

The brain was not examined.

Case 5. This 17 year old white girl was brought to the hospital in coma. She had been in good health save for one episode of dysphagia and regurgitation three years before. Three weeks before admission, she developed a sore throat which persisted for several days. One week later, because of persistent sore throat and fever, her physician prescribed a sulfa-drug which was taken for three days. The family did not recall the specific name of the drug and no information could be obtained from the physician. The patient began to vomit and finally could not retain even fluids. Her mental state was one of confusion progressing to delirium and then coma. Parenteral fluids in undetermined amounts were given without any benefit. No data on the urine output are available. Parotitis developed on the left side. At this time, she was brought from Tennessee to this hospital.

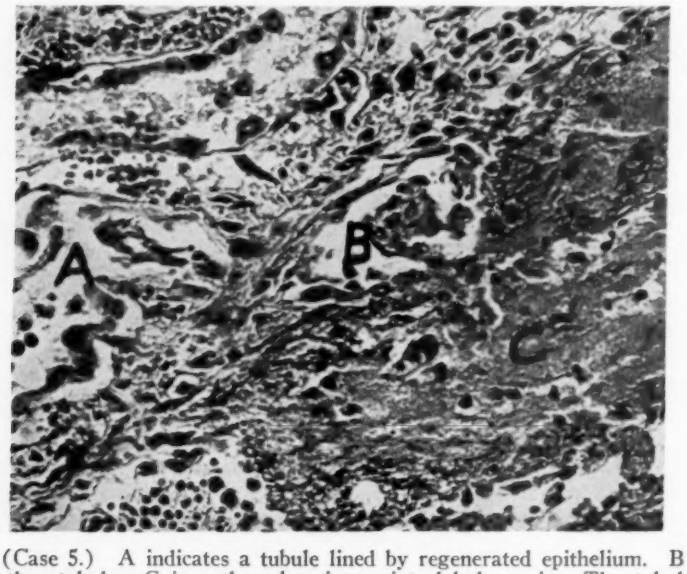

FIG. 3. (Case 5.) A indicates a tubule lined by regenerated epithelium. B shows the lumen of another tubule. C is a thrombus in an interlobular vein. The tubule and vein communicate and epithelial cells are growing in thrombus.

On admission three weeks after alleged sulfonamide medication, the patient was a seriously ill young girl, stuporous and unresponsive. Temperature was 101.8° F., respiration 40, pulse 100, and blood pressure 132 mm. Hg systolic, 90 diastolic. Skin and mucous membranes were dry. The left parotid gland was tensely swollen and pus could be expressed from the parotid duct. Ocular fundi, heart, and lungs appeared normal. Minimal pitting edema was observed over the tibiae. No abnormalities were made out on neurological examination.

Blood examination revealed 4,070,000 red blood cells per cu. mm., with 13,000 white blood cells, of which 93 per cent were granulocytes. Icteric index was normal. Serological tests for syphilis were negative. Urine had a specific gravity of 1.010, was neutral to litmus and contained a trace of protein, a few white blood cells, rare

red blood cells, and rare granular and hyaline casts. No crystals or large casts were seen. Urine volume could not be measured because of incontinence, but was not obviously reduced. Lumbar puncture revealed clear fluid, with no increase in cells or protein. A chloride determination on the spinal fluid could not be titrated, indicating a chloride concentration in excess of 150 m.eq./1.

The patient grew rapidly worse and died 24 hours after admission. She received 5 grams of sodium sulfadiazine intravenously without any obvious effect. Six hours before death, the blood chemistry reports revealed blood nonprotein nitrogen 112 mg. per cent, serum chloride above 150 m.eq./1., carbon dioxide combining power 27 volumes per cent. The patient was given glucose solution intravenously, but the appearance of pulmonary edema prevented the administration of large amounts. At death, blood chemistry revealed nonprotein nitrogen 120 mg. per cent, serum chloride 141.2 m.eq./1., carbon dioxide combining power 26.8 volumes per cent and serum sodium 173.8 m.eq./1. Urine contained 27 m.eq. chloride per liter.

Autopsy. Anatomical Diagnosis: Dilatation and hypertrophy of esophagus; chronic inflammation, edema and small venous thrombi in submucosa of larynx and esophagus; purulent cellulitis, subcutaneous tissues about left parotid gland; ulcerative fibrinopurulent colitis, and edema of stomach submucosa; areas of necrosis of mucosa and submucosa of vagina and cervix uteri; thrombi in intra and extra vaginal and uterine veins; interlobular renal arteries and veins, and adrenal capillaries; emboli in small pulmonary arteries; small infarcts in adrenals (few), and kidneys (many); marked cloudy swelling of renal epithelium and edema of interstitial tissue; necrosis and regeneration of scattered epithelial cells in glomeruli and tubules of kidneys; ascites, hydrothorax, hydropericardium (slight) and pulmonary edema; small area of fibrinous pleurisy, left; edema, gliosis and minute hemorrhages in medulla of cerebellum; fat in liver cells; hemorrhages and marked hyalinization of arterioles in spleen.

Kidneys: Grossly the kidneys were swollen, soft and pale. On the external and cut surfaces there were a good many scattered areas a few millimeters in diameter which were indistinctly outlined, opaque, and partly outlined by reddish borders.

Sections were cut from 20 different blocks of tissue. In 11 sections organizing thrombi were found in interlobular veins or arteries or both. More veins than arteries were occluded. Most of the thrombosed vessels were deep in the cortex and in the boundary zone. Small infarcts, a few millimeters wide, were present in six of the sections. The interstitial tissues of cortex and medulla were coarse meshed and spread apart, due evidently to edema which escaped into the fixing fluids. Damaged tubules, some containing casts and lined by regenerating epithelium, were found to have ruptured into some of the veins which contained thrombi, and the latter showed strands and small masses of proliferating tubular epithelium.

The epithelial cells especially of the glomeruli and of the proximal convoluted tubules showed marked cloudy swelling. Hyaline casts were present in relatively few tubules, most of which were ascending loops of Henle in the cortical rays, but some of the tubules in the pyramids and a few convoluted tubules also contained casts.

Necrotic and regenerating epithelial cells in small numbers were found in glomeruli and in various tubules of cortex and medulla.

Etiology

In the first three cases, sulfathiazole probably precipitated the renal changes which led to the hyperchloremia. These patients were previously active and apparently in good health. Anuria and uremia followed several days of sulfathiazole administration. Hyperchloremia followed as a larger

volume of urine was excreted and as the blood nonprotein nitrogen was decreasing.

In Case 4, there are several possible factors. The patient received many transfusions of stored, citrated blood within a few days. There was transient shock during the hemorrhage. The loss of gastric secretion produced hypochloremia and alkalosis at one time. Finally, the patient received a large dose of sulfathiazole, with high blood levels, crystalluria, and subsequent anuria. As the urine volume increased, the patient developed hyperchloremia. Apparently sulfathiazole precipitated the anuria and subsequent hyperchloremia, but there were other possible factors.

In Case 5, the history was very similar to the other patients', with a rather mild infection said to have been treated with a sulfa-drug, followed by vomiting, stupor, uremia, and terminal hyperchloremia. In view of the ulcerative vaginal lesions and the presence of gross thrombi in pelvic veins, the possibility must be considered that the intrarenal thrombi may have extended up from the pelvic vessels.

Clinical Observations

The first three patients were critically ill during the initial period of anuria and uremia. This was followed by a period of slow improvement, as the uremia subsided. When the serum sodium and chloride concentration rose to excessively high levels, the patients appeared dehydrated, and hyperpnea was noted without a significant decrease in the carbon dioxide combining power of the serum. The mental condition of the patients deteriorated at high serum electrolyte levels. Two patients died with acute pulmonary edema after cautious administration of salt-free fluids at the height of the electrolyte concentration. Two others tolerated a large amount of intravenous fluid and survived.

Three of the patients died before the blood chemistry returned to normal. None of these three patients regained a normal state of consciousness, nor could they speak or make coördinated movements. Because of the chemical disturbances, however, it was difficult to evaluate the mental and neurological changes. Two patients were observed for many weeks after the blood chemistry became normal. They both had persistent difficulty with speech and coördination. Since the neurological changes were most pronounced in a patient who never had a very marked elevation of serum sodium and chloride, the sulfonamide drug may initiate the injury to the central nervous system.

It is worthy of note that the first three patients had a high polymorphonuclear leukocytosis which appeared to be related in time to the sulfathiazole intoxication and not to any obvious infection.

Chemical Changes

The distinctive chemical change was the rapid and unusual increase in serum sodium and chloride concentration. This hyperchloremia was as-

sociated with only a relatively insignificant reduction of serum bicarbonate as measured by the carbon dioxide combining power. There was a gross increase of the total serum electrolyte concentration, normally "one of the most jealously guarded constants of the organism."[1] The high spinal fluid chloride in Cases 3 and 5 indicates that the increased electrolyte concentration was shared by the body fluids other than serum, as might be expected on theoretical grounds.

It may not be assumed that there was a similar increase in the total mass of electrolyte in the body. Indeed, the patients appeared dehydrated at the peak of electrolyte concentration, suggesting a decreased volume of extracellular fluid, which would more or less balance the increased electrolyte concentration. These circumstances suggest that the primary disturbance was a loss of water without a corresponding amount of electrolyte.

The large urine volume of very low, fixed chloride concentration supports the idea that water was being lost in excess of sodium chloride and points to the kidney as the origin of the disturbance. In one patient a mannitol clearance test, performed while the electrolyte disturbance was subsiding, showed a reduction of glomerular filtration to 30 per cent of normal. Simultaneous determination of serum and urine chlorides indicated that 97 per cent of the chloride in this glomerular filtrate was reabsorbed, whereas only 90 per cent of the water was reabsorbed. These data, suggesting a greatly reduced volume of glomerular filtrate and a failure of the tubules to reabsorb the normal proportion of water, afford a plausible explanation for the large volume of urine of very low salt content.

The rise of serum chloride concentration above normal was observed only after the daily urine output became large. For the first week in the hospital, Cases 1 and 2 received considerable amounts of salt and water to overcome the initial dehydration and oliguria. The serum chloride remained low, since the fluids given were hypotonic and the oliguric kidney could exert little influence on the composition of the body fluids. When the urine volume increased, the blood nonprotein nitrogen began to fall, and simultaneously the serum chloride rose.* There was no superficial change in the character of the urine which remained dilute and neutral in reaction.

It would therefore seem that the large amounts of salt and water given to several anuric patients had little effect on the subsequent rise of serum sodium and chloride concentration. The rise was dependent on the secretion of a large volume of urine, with excessive loss of water without salt in the urine and the failure to replace this water without salt. Under these conditions, the serum electrolyte concentration must increase regardless of the previous state of hydration. Any salt given after the urine volume becomes large, however, definitely aggravates the electrolyte disturbance.

Serum electrolyte changes of the type and degree seen in these patients are not ordinarily observed in chronic nephritis. Hyperchloremia is un-

* In Cases 1, 2, and 3. In Case 4 the blood nonprotein nitrogen was difficult to interpret because of gastrointestinal hemorrhage. In Case 5, data are not available.

common in chronic retentive nephritis, and serum base concentration is almost without exception normal or low.[2] Slight elevation of the serum chloride concentration is the rule in the nephrotic syndrome but is not accompanied by any appreciable increase in serum base concentration.[3] If an adequate fluid intake is maintained, excessive salt intake does not ordinarily raise the serum chloride concentration except as it displaces bicarbonate, with the serum sodium concentration approximately normal. In other words, even in severe chronic nephritis, when sodium chloride is retained in the body a proportional amount of water is retained with it so as to keep the concentration of sodium near normal. Retention of salt thus results in edema rather than hyperchloremia. This relationship was lost in the patients here reported in whom water was lost so much in excess of salt. To be sure, in severe chronic nephritis with a normal serum concentration, the maximum urinary chloride concentration is usually considerably higher than in the cases here reported, though rarely approaching the serum concentration.[4]

Although the rapid onset, the extreme degree of hyperchloremia and the very high serum sodium levels in these patients are unique, other cases with some points of similarity have been described. Butler, Wilson and Farber[5] described persistent dehydration with hyperchloremia in infants. These changes were chronic and were associated with acidosis and no elevation of serum sodium. Calcification was found about the kidney tubules. Butler, Wilson and Farber[5] and Albright, Consolazio, Coombs, Sulkowitch and Talbot[6] have reported similar changes in older children, associated with rickets and dwarfism. In most of these patients, the cause of the calcification about the kidney tubules was not known. In one case, hyperparathyroidism was apparently the initiating factor. The most extensive calcification in all of these patients was about and within the collecting tubules, although some changes were evident in other portions of the tubules.

Discussion of Renal Lesions

Hematuria, oliguria and azotemia have frequently been observed in man and in experimental animals following the administration of sulfonamides; and these signs and symptoms, when investigated, have usually been found to be associated with obstruction due to precipitation of crystals in renal tubules or ureters, or in both.

The occurrence of high serum sodium and chloride concentrations after sulfonamide medication, developing and progressing while azotemia and oliguria decreased, has not been described before. Such a specific functional disturbance suggests a corresponding specific renal lesion, and the changes found in the kidneys of Cases 1 and 2 point to the intercalated segments of the distal convoluted tubules, the spiral portions of the proximal convoluted tubule, the collecting cortical tubules, or the ascending limb of Henle's loop as possible sites of the specific disturbance. In the other two cases which

were examined microscopically it was impossible to correlate the salt retention with specific localized lesions.

The occurrence of thrombi in intrarenal veins (Cases 1 and 5) due to sulfonamide administration has not been described before in man. It has been seen in the monkey following sulfapyridine medication [7] and in dogs which were given sulfadiazine.[8]

In one of our cases (Case 1) in which thrombi formed in the intrarenal veins, the only sulfonamide given to the patient was sulfathiazole. This is of some interest because Climenko and Wright [7] found renal thrombi in their monkeys after sulfapyridine, but never in the sulfathiazole animals. In our other case (Case 5) which showed thrombi in renal vessels, the exact nature of the sulfonamide which the patient took, and the dose could not be determined, and thus it is possible that the lesions found were due to some other drug. Moreover, there were thrombi in many small renal veins and arteries, and there were thrombi in vessels other than those in the kidneys. Most of the changes in the kidneys themselves were probably caused solely by the vascular occlusions.

The damaged and ruptured tubules in the boundary zone, associated with thrombosed interlobular veins and with proliferating tubular epithelium in the thrombi (Cases 1 and 5), are apparently identical with similar lesions described by Dunn, Gillespie, and Niven [9] as occurring in two cases of crush syndrome. One of these patients lived for nine days and was treated with sulfapyridine. This report does not state whether the second patient received sulfonamide medication, but it would seem possible that these tubulovenous lesions may have been related to the therapy rather than to the crushing injuries.

The pathogenesis of intrarenal thrombus formation following sulfonamide therapy is not clear, but it may be suggested that precipitated crystals could easily project through the tubular epithelium and into the very thin walled interlobular veins, and in this way might cause thrombi to develop.

Treatment of Electrolyte Disturbance

During the stage of anuria, there is little danger of hyperchloremia. The use of very hypotonic fluids at this time serves only to depress the already low electrolyte concentration. A slightly hypotonic mixture of sodium chloride and lactate, with glucose as needed, seems to be effective.

As the urine volume increases, the fluid intake should be maintained at a level of at least 3000 c.c. a day. Salt intake should be eliminated. In some cases a large volume of intravenous salt-free fluid may be needed daily to avoid hyperchloremia.

Not every patient with sulfathiazole-induced oliguria develops hyperchloremia. On the other hand, when symptoms become prominent, the hyperchloremia is already far advanced and treatment may be ineffectual. The ideal method is to follow the serum chloride concentration.

Summary

1. Three patients with severe sulfathiazole intoxication and two patients with probable sulfonamide poisoning are described.

2. All of the patients developed an unusual increase in serum sodium and chloride concentration. When continuous observations were made, the electrolyte disturbance appeared while oliguria and nitrogen retention diminished. The excessive height of the serum electrolyte concentration probably contributed to the death of two patients.

3. The renal lesions found in two cases suggest that the dissociation of salt and water excretion may be related to changes in certain specific portions of the tubule.

4. There were thrombi in interlobular veins in two cases. In one of these, thrombi in both interlobular arteries and veins were numerous and probably produced the renal lesions recognized in this case. In both cases, the thrombosed veins were associated with ruptured tubules and the proliferation of tubular epithelium in the thrombi. Both patients developed moderate hypertension.

5. Clinically, there was evidence of cerebral damage. In the two patients who survived the uremia and hyperchloremia, the signs of injury to the central nervous system persisted, with slow and incomplete recovery. In the brains which were examined, areas of edema and gliosis were found, together with small hemorrhages in one case.

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LEUKEMIA: THE RELATIVE INCIDENCE OF ITS VARIOUS FORMS, AND THEIR RESPONSE TO RADIATION THERAPY *

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Were one resigned to the acceptance of the cause and cure of leukemia as a problem of the inscrutable future, requiring for its solution weapons not yet conceived in imagination, then the study of the cytologic features underlying its varied clinical manifestations would constitute little more than an exercise in morbid histology. If, on the other hand, one believes that an understanding of the cell types involved in leukemic change is a prerequisite to the progressive clarification of the problem in its entirety, then detailed cytologic analysis becomes a potentially profitable undertaking.

The purpose of this communication is to present a series of cases of leukemia, all of which have been subjected to the same criteria of differentiation, and to indicate the relative frequency of the several types of cellular involvement which have been observed. Consideration is also given to the sex and age incidence and to the degree of response of the patients' disease to radiation therapy, but detailed presentation of clinical information and quantitative blood changes is deferred for later publication.

The series to be reported is composed of 495 cases examined at the Simpson Memorial Institute between July 1, 1927 and December 31, 1941, a period of 14½ years. For the purposes of this and subsequent studies the records of all the patients were analyzed and data supplied by the history, physical examination and laboratory procedures, including biopsy and necropsy, were tabulated. In 262 cases, including those in which the original diagnosis appeared to be in reasonable doubt, the blood and, when available, the marrow films were reëxamined. In 19 per cent of the cases necropsy was performed and the presence of leukemia was confirmed, although designation of specific type, as here reported, was not usually made. Lymph node biopsy was performed in only a negligible number of instances, except in cases of lymphosarcoma cell leukemia. Marrow was examined during life in but a few instances prior to 1936. After this date such study was carried out in practically every case, except in young children with leukemic lymphoblastic leukemia and in patients with lymphocytic and myelocytic leukemia in leukemic phase. Of these groups marrow examinations were made in about half the cases.

It has seemed possible to classify the great majority and perhaps all of the cases observed according to three parent cell types: the lymphoblast, the myeloblast, and the undifferentiated or but slightly differentiated reticulum

* Read at the St. Paul meeting of the American College of Physicians April 20, 1942.
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cell (histioblast or histiocyte). These main divisions of leukemia are designated, respectively, as lymphogenous, myelogenous and histogenous (chart 1). The subdivision of lymphogenous leukemia into lymphoblastic, lymphocytic, and lymphosarcoma cell types, has been discussed in an earlier communication, and these forms of the disease will not be considered here, except for purposes of comparison.[1]

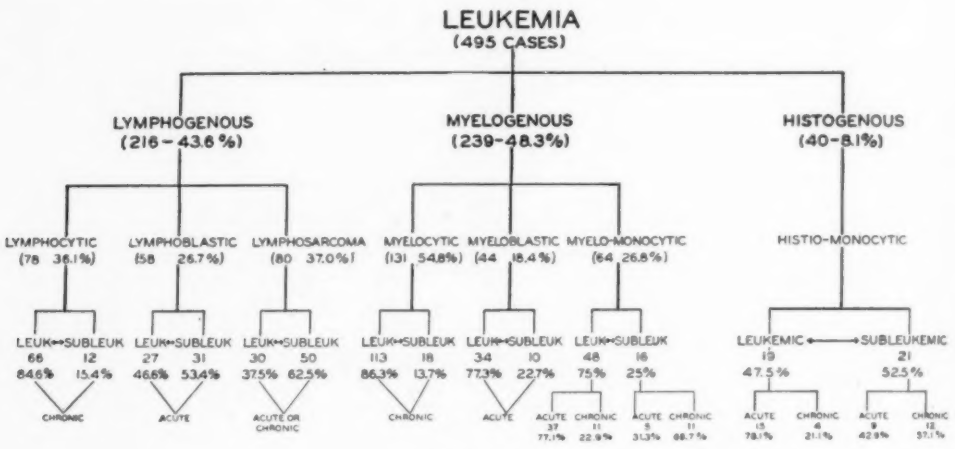


CHART 1.

The consideration of varieties of myelogenous leukemia is based on the view expounded by Naegeli,[2] and supported by observations made on the patients of this series, that the myeloblast, or its immediate precursor, the micromyeloblast, may undergo leukemic proliferation with little or no evidence of maturation, or there may be development into the myelocyte and later stages, or there may be transition to the monoblast with subsequent formation of older forms of the monocyte series. These three forms of myelogenous leukemia are termed, respectively, myeloblastic, myelocytic and myelomonocytic. Most of the rarer forms of leukemia, such as erythroleukemia, and eosinophilic, basophilic, and probably megakaryocytic leukemia are members of the myelogenous group. Plasma cell leukemia, on the other hand, as suggested by Richter [3] may be related to the lymphogenous types.

There remains a group of cases of leukemia which exhibit no evidence of lymphoblastic or myeloblastic involvement, but are characterized by generalized proliferation of cells of reticuloendothelial origin. Monocytes in their several stages of development are commonly found in the circulating blood of such patients, and frequently there also occurs larger "histiocytic" forms. This type of leukemia is here called histiomonocytic (figure 1).

A critical discussion of monocytic leukemia with a review of the very extensive literature on the subject is given by Downey.[4] That form which is believed to arise from the myeloblast he designates as the Naegeli type,

whereas leukemia of reticuloendothelial origin is termed the Schilling type of monocytic leukemia. According to Downey, "The end products (ripe monocytes) might have identical morphology but the intermediate and younger forms would be different." However, accurate diagnosis often requires marrow examination and one hesitates to identify a case of leukemia as of histiomonocytic type without pathologic evidence of ungoverned reticulum cell hyperplasia.

Watkins and Hall [5] have adopted Downey's differentiation of monocytic leukemia and in accordance with it have classified the cases seen at the Mayo Clinic during a 10 year period. These authors describe in detail the

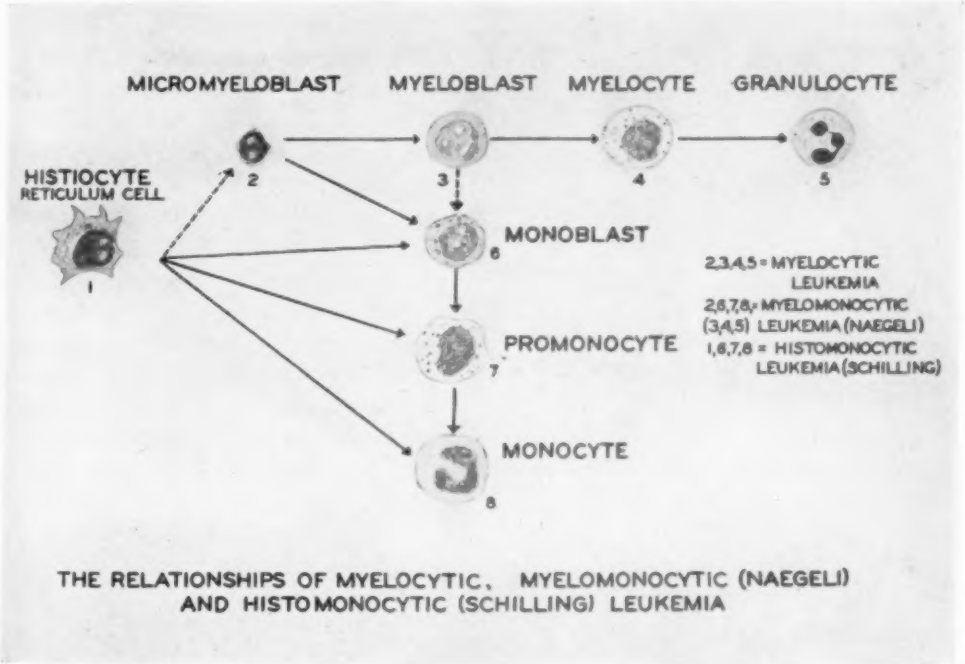


FIG. 1.

morphology of the cells seen in both types of monocytic leukemia, as well as marrow changes characteristic of the two diseases. In general, the peripheral blood in cases of myelomonocytic leukemia (Naegeli) contains a predominance of monocytes in various stages of maturity together with a small (sometimes large) number of myeloblasts and young myelocytes. Monoblasts differ from myeloblasts, in Wright stained films, in that the nuclear chromatin of the former is arranged in a fine transparent network, the nucleoli are quite inconspicuous and the cytoplasm is more plentiful and often contains fine red granules at a stage of nuclear development when granulation is not found in the myeloblast. In histiomonocytic leukemia (Schilling) myeloblasts are absent from the peripheral blood, although an

occasional myelocyte may be found. Monocytes, often quite mature in appearance, predominate, and larger histiocytes may be present. In the latter, the chromatin of the nucleus is arranged in a relatively coarse network, the nucleoli are indistinct in the earlier forms but small and clearly outlined in the later stages. The cytoplasm is blue-gray and often contains

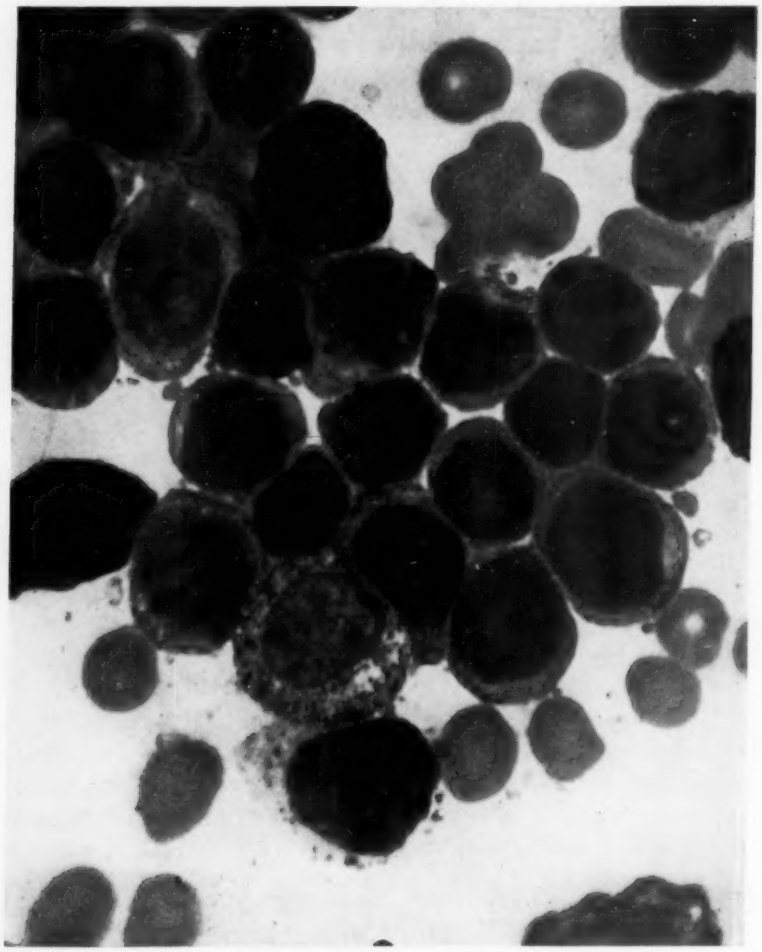


FIG. 2. Myeloblastic leukemia. The predominating cells are myeloblasts; a few young myelocytes are present. Aspirated sternal marrow. Wright's stain. × 920.

dense, fine, brick-red granulation. In marrow films the cytoplasm of the histiocytes is usually abundant, but in the case of cells obtained from the circulating blood it may be quite scanty and irregular.

Instances of leukemia classified under the several types mentioned have been further subdivided in accordance with quantitative changes of leukemic cells at the time when the patients were first observed. The blood picture

is termed subleukemic when at least 10 per cent of the circulating white cells exhibit a specific type of abnormality on which the morphologic diagnosis is based, but the total of such cells does not exceed 10,000 per cubic millimeter. The condition is considered leukemic when the number of cells exhibiting the type-specific abnormality exceeds 10,000 per cubic millimeter. It is to be emphasized that such a distinction is arbitrary, and that transition from one phase to the other is frequently observed. Nevertheless, separate consideration of instances of subleukemic leukemia is justified for two reasons. First, in the more acute types of leukemia, but not usually in the chronic forms, an unelevated white blood cell count portends, as a rule, a

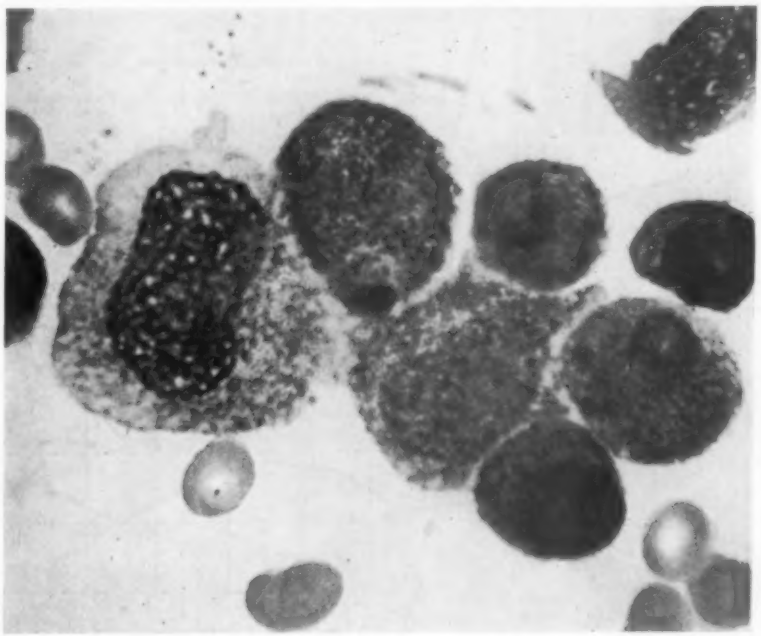
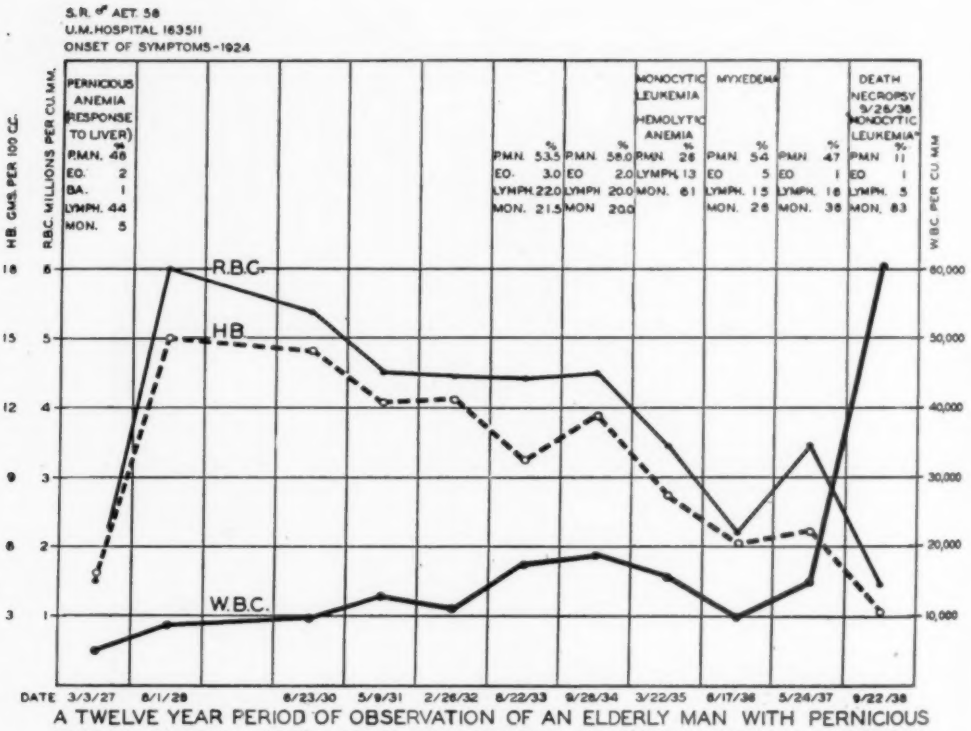


FIG. 3. Acute subleukemic histiomonocytic leukemia. The cells are all histioblasts or histiocytes. Aspirated sternal marrow. Wright's stain. × 920.

longer duration of life. Second, it is in the presence of a subleukemic blood picture that an erroneous diagnosis is most likely to occur. Leukopenia, or a leukocyte count within the normal range, is observed least often in the commonest form of leukemia, the myelocytic. Moreover, whereas subleukemia of the lymphogenous or histogenous type is apt to be overlooked, the diagnosis of subleukemic myelogenous leukemia is frequently mistakenly made. Such cases usually represent instances of leukopenic leukemoid reactions in the presence of neoplastic invasion of the marrow, or of miliary tuberculosis, or they fall in the ill-defined group of non-leukemic myeloid metaplasias.[6, 7]

The difficulties involved in the diagnosis of subleukemic histiomonocytic leukemia, and particularly its differentiation from non-leukemic reticuloendotheliosis, have been thoroughly discussed by Downey[4] and by Jaffe.[8] The patient who supplied the data presented on chart 2 was observed by Dr. Raphael Isaacs for several years in subleukemic phase before developing leukocytosis.[9] The case is similar to that reported by Derischanoff,[10] who regarded his patient as manifesting generalized non-leukemic reticulum



A TWELVE YEAR PERIOD OF OBSERVATION OF AN ELDERLY MAN WITH PERNICIOUS ANEMIA, CHRONIC HISTIO-MONOCYTIC LEUKEMIA, HEMOLYTIC ANEMIA & MYXEDEMA

CHART 2.

hyperplasia in the presence of Addisonian pernicious anemia. Dr. Isaacs' patient revealed at necropsy such generalized and characteristic infiltrative changes that to question the leukemic nature of the process would imply more definite criteria for the diagnosis of leukemia than are possessed. This case is believed to represent an instance of chronic histiomonocytic leukemia, the existence of which in the non-acute form has been denied by Jaffe.[8] The majority of patients with histiomonocytic leukemia, both subleukemic and leukemic, in the series herein reported, experienced acute illness with early death, although Watkins and Hall report a predominance of the chronic form of the disease in their cases.

The age ranges of the patients comprising this series, at the time of onset of their symptoms, are shown on chart 3. Cases of lymphogenous leukemia are excluded since data pertaining to them have been previously reported. After the age of 20, myeloblastic leukemia replaces lymphoblastic as the most common of the acute leukemias. It is believed, in agreement with Wintrobe,[11] that little purpose is served by the classification of

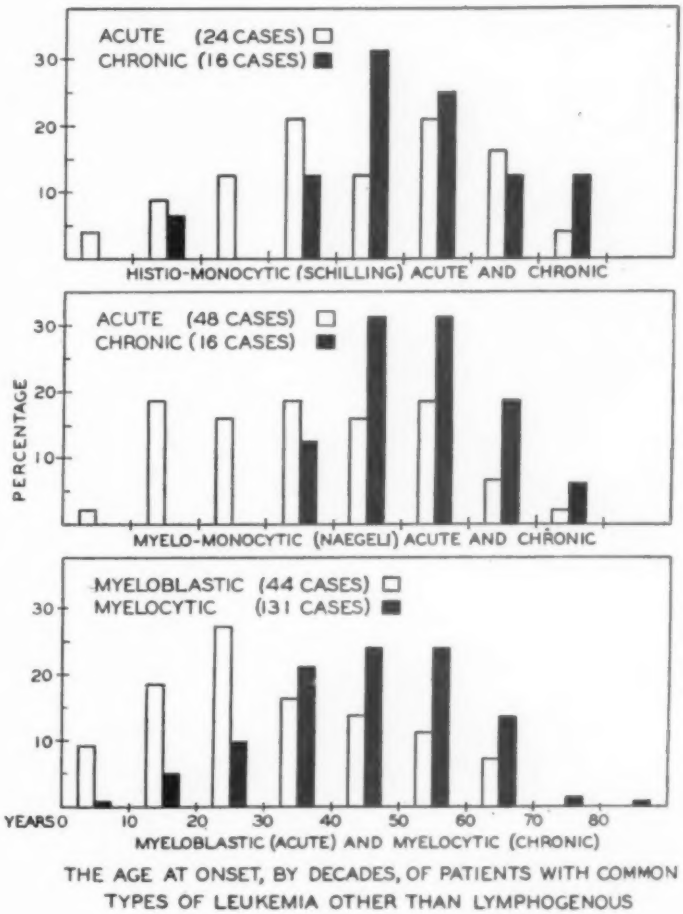


CHART 3.

cases of leukemia as subacute, since their resemblance to the acute form is much closer than to the chronic. Among the chronic forms of the disease the myelocytic predominates until the seventh decade is reached when the lymphocytic type is most frequently observed. These findings are in essential agreement with those reported by Ward,[12] Minot and Isaacs,[13] Minot, Buckman and Isaacs,[14] Leavell,[15] Rosenthal and Harris,[16] and Wintrobe and Hasenbush.[17] Chronic monocytic leukemia, of both myelogenous and

histogenous types, was most often encountered between the ages of 40 and 60, whereas the incidence of the acute forms was more evenly distributed, except at the extremes of life. This age incidence conforms with that of the cases collected by Osgood.[18]

Several writers have commented on the apparent increase in the incidence of leukemia, attributing it, usually, to the more widespread use of

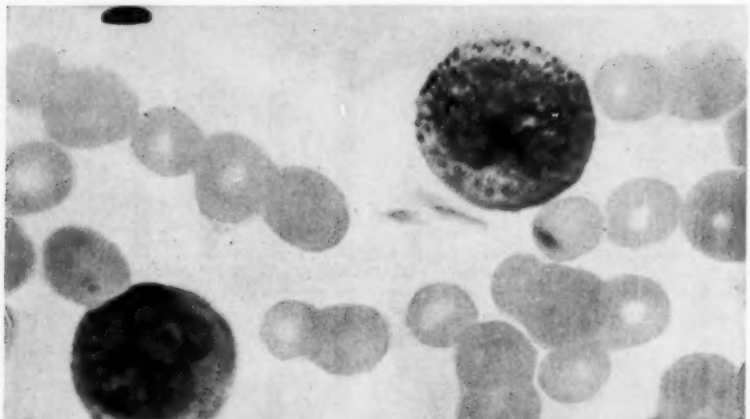


FIG. 4. Acute leukemic histiomonocytic leukemia. The cells are monocyte types. Blood film. Wright's stain. × 920.

diagnostic laboratory procedures. Lucia,[19] however, believes that the increase is an actual one. With this problem in mind, the patients of this series have been grouped in five year periods according to the date of their first observation at the Simpson Memorial Institute. The periods extend from 1927 to 1941 inclusive (table 1). Comparatively few cases of all types were seen in the year 1927, but taking this fact into consideration, there

TABLE I

The Sex and Median Age and Relative Frequency of the Several Types of Leukemia, and Their Apparent Increasing Incidence

	Per Cent Males	Median Age at Onset (Approx.)	Incidence 1927–1931		1932–1936		1937–1941		Total	
			No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent
		Years								
Myelocytic	51.9	46	27	20.6	46	35.1	58	44.3	131	26.5
Myeloblastic	68.2	24	6	13.6	14	31.8	24	54.5	44	8.9
Myelomonocytic (chronic)	59.1	51	5	22.7	7	31.8	10	45.5	22	4.4
Myelomonocytic (acute)	52.4	32	3	7.1	12	28.6	27	64.3	42	8.5
Histiomonocytic (chronic)	87.5	45	3	18.8	5	31.2	8	50.0	16	3.2
Histiomonocytic (acute)	62.5	29	2	8.3	7	29.2	15	62.5	24	4.8
Lymphogenous (all types)	—	—	53	24.5	65	30.1	98	45.4	216	43.6
Total	—	—	99	20.0	156	31.5	240	48.5	495	99.9

has been a progressive increase in patients suffering with leukemia in comparison to those on whom diagnoses of other blood disorders have been made. Two reasons which no doubt partially explain this change are evident. Referring physicians, from whom all of our patients are obtained, are diagnosing and treating more patients with various forms of anemia than they did formerly, and at the same time are recognizing and referring cases of leukemia. Few practitioners, however, undertake, without consultation, the management of thrombopenic purpura or hemolytic jaundice, and there has been little or no change in the relative incidence of these diseases throughout the past 15 years. The second possible explanation for the progressive increase in cases diagnosed as leukemia lies in the current use of sternal marrow examination in practically every patient with a suspected primary blood disorder. Undoubtedly, this procedure accounts for the recognition of an appreciable number of cases of subleukemic leukemia, but it cannot explain the almost equally great increase in the number of patients with the leukemic forms of the disease. Of special significance is the larger group suffering with acute leukemia, as compared to those with the chronic type, and the more frequent occurrence of the monocytic forms. It seems probable that the increased incidence of chronic leukemia is merely apparent and can be explained by the reasons given above, but on the other hand it is believed that there is an actual increase in acute leukemia.

The results of treatment by roentgen irradiation are shown in table 2. The plan of therapy has involved, in almost all cases, an intensive short course of treatments with exposure limited usually to the splenic area in cases of myelocytic and chronic myelomonocytic leukemia. Two hundred kilovolts and 25 milliamperes are generally used, with distance of 50 cm.,

TABLE II

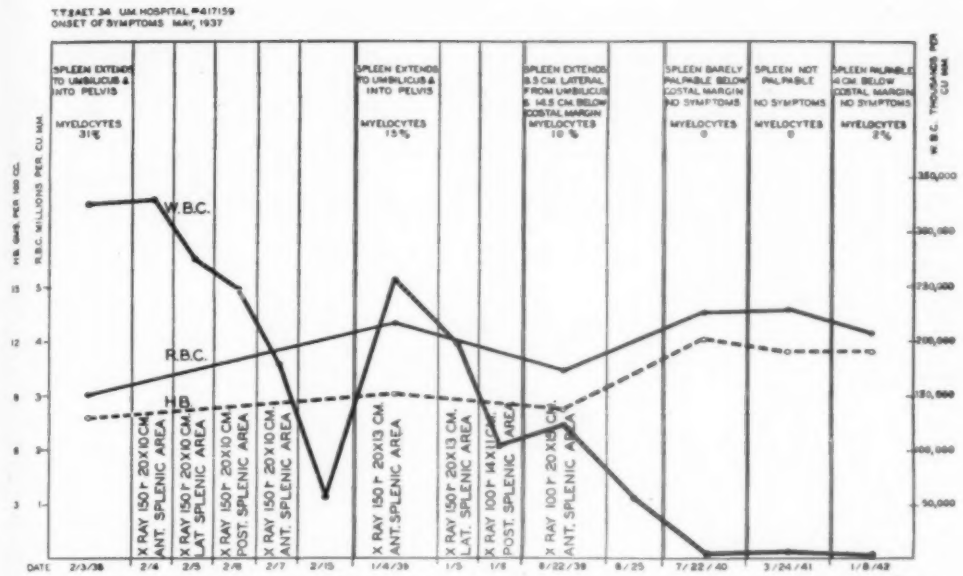
Response to Intensive Short-Course Roentgen Therapy in Cases of Leukemia*

Type of Leukemia	Total Number	Unfavorable		None		Fair		Good		Very Good		Excellent	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Myelocytic	104	0	0.0	2	1.9	8	7.7	38	36.5	43	41.3	13	12.5
Myeloblastic	16	5	31.3	9	56.3	2	12.5	0	0.0	0	0.0	0	0.0
Myelomonocytic (chronic)	17	0	0.0	5	29.4	5	29.4	5	29.4	2	11.8	0	0.0
Myelomonocytic (acute)	8	3	37.5	4	50.0	1	12.5	0	0.0	0	0.0	0	0.0
Histiomonocytic (chronic)	6	0	0.0	2	33.3	0	0.0	3	50.0	1	16.7	0	0.0
Histiomonocytic (acute)	1	0	0.0	1	100.0	0	0.0	0	0.0	0	0.0	0	0.0
Lymphocytic	50	0	0.0	2	4.0	6	12.0	10	20.0	13	26.0	19	38.0
Lymphosarcoma Cell	52	12	23.1	10	19.2	13	25.0	6	11.5	6	11.5	5	9.6
Lymphoblastic	10	3	30.0	4	40.0	3	30.0	0	0.0	0	0.0	0	0.0

* Unfavorable, exacerbation of leukemic process with early death; none, course of disease apparently unaltered; fair, transient clinical improvement but no real remission; good, significant clinical and hematologic improvement lasting three to six months; very good, lasting six to 12 months; excellent, lasting more than 12 months.

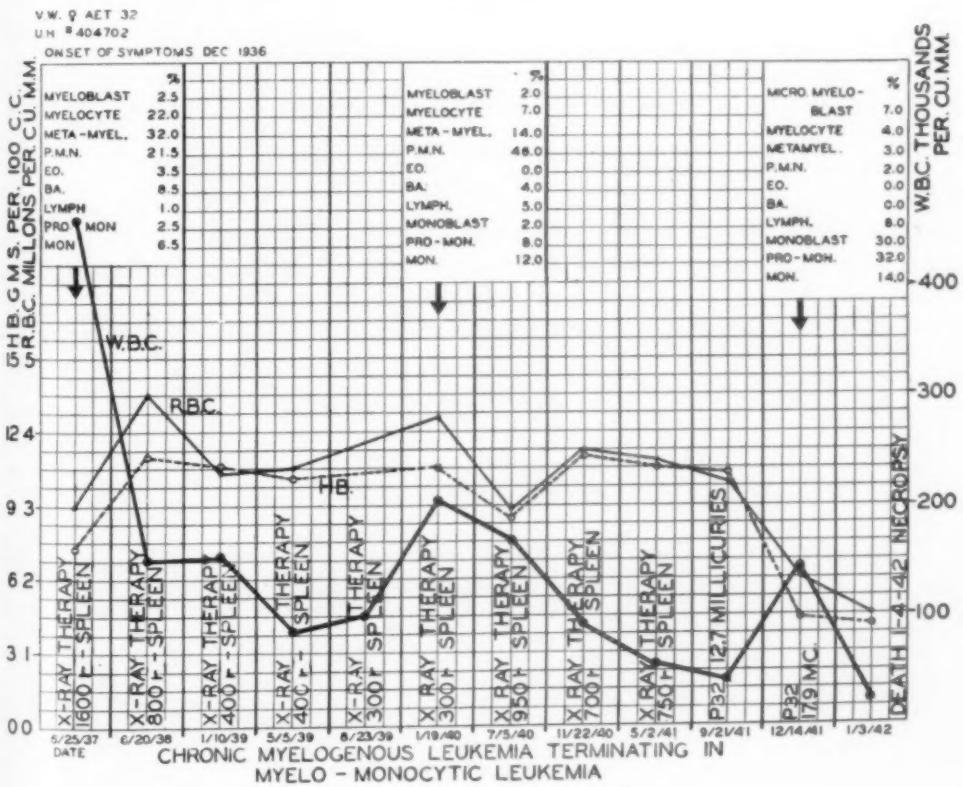
copper filter, .5 mm., aluminum filter, 1 mm., size of field 10 by 10 to 15 by 20 cm., skin dose 100 to 200 roentgens to each field, with a total of 3 to 5 fields over the anterior, lateral and posterior surfaces of the splenic area. Treatments may be given on consecutive days and in any case are preferably carried out as rapidly as possible (Isaacs [20]), except that not more than one field is treated during a 24 hour period. It should be emphasized that not all patients will tolerate the maximum treatment outlined above, and that the reaction is often unpredictable. Therefore, at the outset, smaller doses and more limited fields should be employed.

The indications for radiation therapy in myelocytic and myelomonocytic leukemias are symptoms of anemia, of increased metabolism, of pressure from splenomegaly, and of pain in or referred from the splenic area. In the absence of disabling symptoms therapy is deferred. The level of the leukocyte count at the time of institution of treatment bears little relation to the indication for its use, but the rapidity of decline of the white blood cell count is a useful guide to its continued employment. As many observers have pointed out, and as the data here presented indicate, the value of radiation therapy is limited to patients with the chronic forms of leukemia. Best results are obtained in the myelocytic and lymphocytic varieties, but the degree of improvement, the duration of the remission, and the time which will elapse before the occurrence of a refractory state cannot be foreseen in any individual case.



UNUSUALLY GOOD RESPONSE TO ROENTGEN THERAPY EXHIBITED BY A YOUNG WOMAN WITH MYELOCYTIC LEUKEMIA

CHART 4.



CHRONIC MYELOGENOUS LEUKEMIA TERMINATING IN MYELO - MONOCYTIC LEUKEMIA

CHART 5.

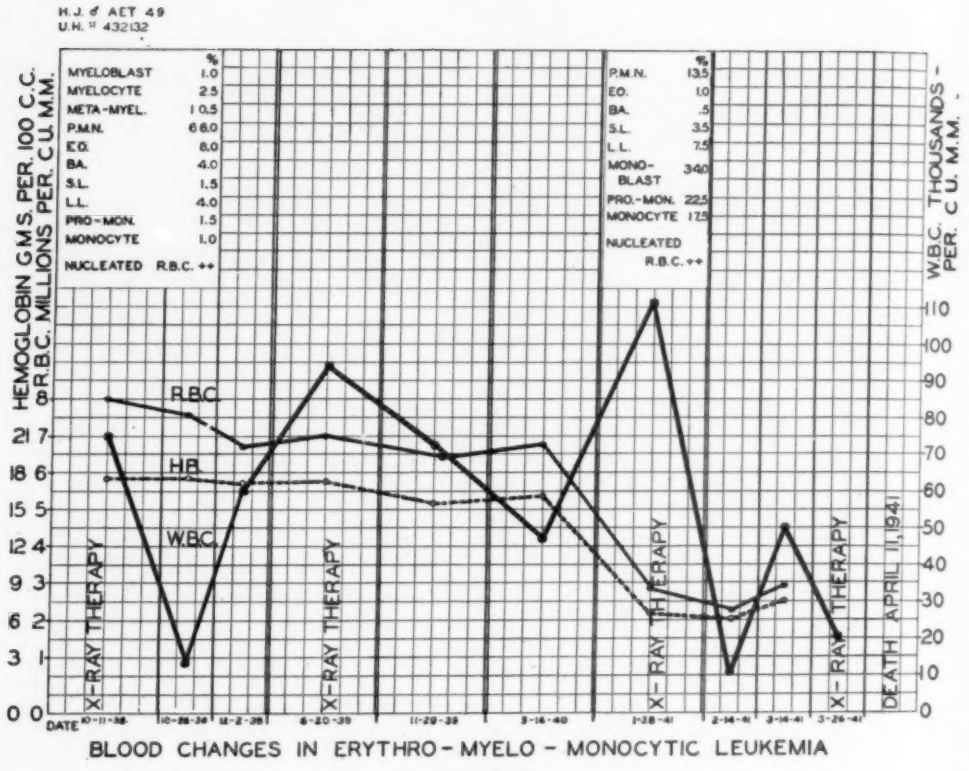


CHART 6.

Illustrations of response to radiation therapy are provided by the patients supplying the data shown on charts 4, 5 and 6. In the first instance a remarkably fine result was obtained, and for a period of two years the patient, suffering with myelocytic leukemia, was entirely free from subjective and objective manifestations of the disease. At present, she is symptomatically well, but the presence of myelocytes in the peripheral blood and the slight but demonstrable increase in the size of the spleen indicate the beginning of exacerbation.*

The second patient demonstrates the more usual type of response to radiation, but her case is worthy of special note because it is an instance of transition from the myelocytic to the myelomonocytic type of leukemia, as previously reported by Craciuneaunu and Calalb [21] and by Hall and Watkins.[22] Such cases emphasize the close relationship of this form of monocytic leukemia to the myeloblastic developmental series.

The third case is of particular interest. The patient was first seen in 1938 and at that time he exhibited polycythemia with many circulating late

* This patient died on Sept. 2, 1942 in an acute subleukemic exacerbation of his disease. The terminal blood values were as follows: R.B.C. 1,400,000 per cu. mm., hemoglobin 3.8 grams per 100 c.c., hematocrit 13.0 per cent, W.B.C. 500 per cu. mm., of which practically all were myeloblasts. No roentgen therapy had been given since August, 1939.

normoblasts, and a myelocytic leukemia type of leukocyte picture. Sternal aspiration revealed an extremely cellular marrow with active, but not apparently abnormal, erythropoiesis and granulopoiesis. Although, on re-examination of these films, monocyte developmental forms could be identified, at the time of the initial study they were not sufficiently conspicuous to occasion special note. A good result was obtained from radiation therapy, but when the patient returned in 1941, after an interval of eight months, a

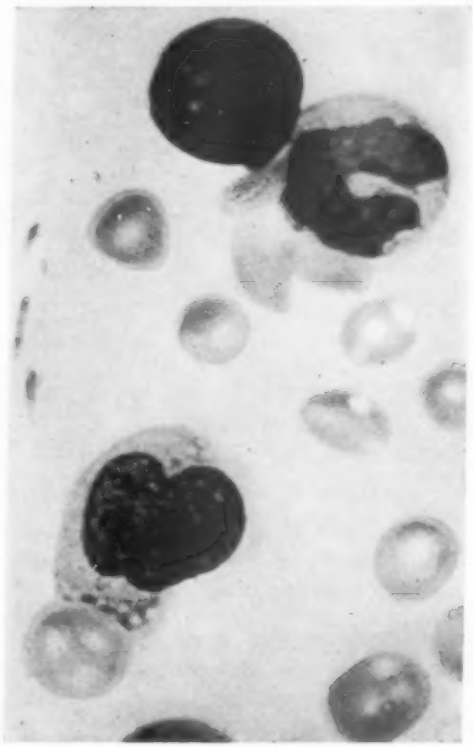


FIG. 5. Myelocytic leukemia terminating in myelo-monocytic leukemia (patient V. W., chart 5). From above down the cells are, respectively, a myeloblast, a monocyte, and a promonocyte. Blood film. Wright's stain. × 920.

great change was noted both in the peripheral blood and marrow. Anemia was severe, and the leukocytes were predominantly of the monocyte series with 34 per cent in the blast stage of development. The marrow did not reveal displacement of erythrocyte forming tissue, but instead proliferation of early basophilic erythroblasts with very little evidence of maturation. These cells did not resemble megaloblasts, but possessed many of the features of the marrow cells seen in cases of Cooley's anemia. Concurrently there were observed, in separate groups, all stages of monocyte development with mitotic figures fairly common. Typical myeloblasts and myelocytes were

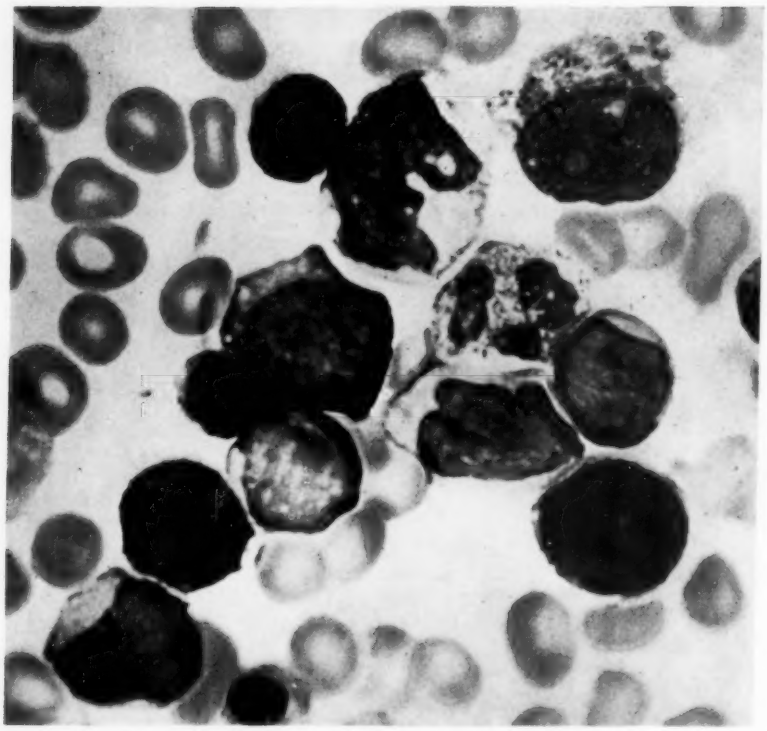


FIG. 6. Erythro-myelo-monocytic leukemia (patient H. S., chart 6). The cell at upper right is a histiocyte, probably not directly involved in the leukemic process. Below it is a neutrophile. The cells with darker nuclei are members of the erythrocyte series. The others are all developmental forms of the monocyte. Aspirated sternal marrow. Wright's stain. × 920.

almost absent. Unfortunately, this man died at home, after failing to benefit from roentgen therapy, and necropsy was not obtained.

CONCLUSIONS

A series of 495 cases of leukemia is reported with respect to the sex and age incidence and the relative frequency of the various types.

Particular emphasis is placed on the differentiation of monocytic leukemia related to the myeloblast and that form believed to arise from an undifferentiated reticulum cell or histioblast.

The relative and absolute increase in the acute forms of leukemia observed in recent years is believed to indicate a greater incidence of such diseases.

Roentgen therapy of leukemia is discussed and the results of such treatment are presented.

Hematologic data on four illustrative cases of leukemia are reported.

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EXPERIMENTAL STUDIES ON HEPARIN AND ITS INFLUENCE ON TOXICITY OF DIGITALOIDS, CONGO RED, COBRA VENOM AND OTHER DRUGS *

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Introduction

At first engaging the attention primarily of physiologists and hematologists, the study [1, 2, 3] of heparin was soon taken up also by biochemists, who of recent years have succeeded largely in unraveling its complicated chemical structure. More recently, heparin has acquired a practical significance through the work of clinical investigators who discerned its potentialities as a therapeutic agent. Indeed, Howell and McDonald [4] had suggested such clinical applications of heparin, but its actual value in medical practice was not demonstrated until the painstaking investigations of American, Canadian and Swedish scientists were well under way. It is far beyond the scope and aim of this paper to cite the complete literature, which may be gleaned from Jorpes' excellent monograph [5] and Mason's comprehensive review [6] of the subject. Clinically heparin has been advocated especially as a prophylactic agent against thrombo-embolic complications of various kinds. Among the earlier contributions to the subject may be mentioned the work of Crafoord [7, 8] and the brilliant experimental research on animals as well as clinical contributions of Murray, Jaques, Perrett, Best [9, 10] and Solandt.[11] This work demonstrated the usefulness of heparin in preventing the formation of clots in blood vessels in animals as well as the smaller incidence of thrombo-embolic complications in postoperative treatment of human patients. More recent clinical papers on the subject have been published by Crafoord, Jorpes and Best.[12, 13, 14] Leissner [15] used heparin in obstetric practice for preventing thrombosis and Clason [16] reports the results obtained with this drug in three cases of pulmonary embolism. In the ophthalmological field prevention of thrombosis in retinal veins has been reported by Ploman,[17] Holmin,[18] Boström and William-Olsson [19] and, more recently, by Ferguson.[20] An attempt to combine heparin with various chemotherapeutic agents in the treatment of bacterial endocarditis has been described by Kelson,[21] and more recently by a group of clinicians in Boston.[22] No longer now of merely physiological and biochemical interest, heparin merits a place with the newer pharmacotherapeutic agents. A comprehensive pharmacological study of this substance was, therefore, deemed desirable

* Received for publication December 22, 1942.
Read before the Section on Pathology and Physiology of the American Medical Association at Atlantic City, June 11, 1942.

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and in the following pages the writer purposes to report new experimental observations on the subject.

Chemistry of Heparin. Although not yet completely solved, the chemistry of heparin is now pretty well known, thanks to the work of numerous investigators and especially of Charles and Scott,[23] Bergström, Jorpes and Wilander,[24] and Chargaff.[25] Heparin is a mucoitin polysulfuric acid with not less than 40 per cent of sulfuric acid. Being a polysaccharide, it possesses an extremely high negative electric charge, which is probably responsible largely for its reaction with other compounds playing a rôle in the coagulation system. In fact, heparin may be regarded as a sort of hormone regulating the blood coagulation and like the hormones it is produced by a special kind of cell, i.e., the so-called mast cells of the connective tissue, found mainly in vicinity of capillaries and blood vessel walls. Heparin is thought to pass from these cells either directly or by diffusion into the blood stream. The so-called metachromatic granules of these cells, consisting of heparin, exhibit characteristic staining reactions.[26]

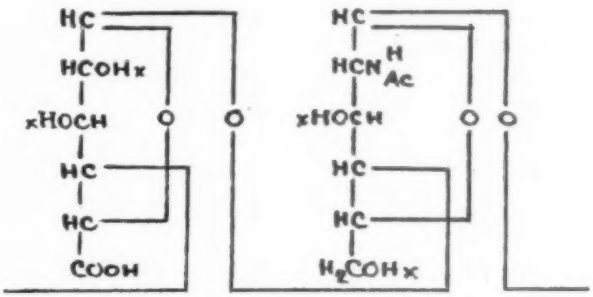

FIG. 1. The organic moiety of heparin, mucoitin = glucuronic acid + acetylated glucosamine.

The heparin employed in the present experiments was prepared in our chemical research laboratory. As a matter of historical record, it may be stated here that this was the first chemical research laboratory to produce heparin for Professor William H. Howell, who 20 years ago entrusted Dr. H. A. B. Dunning with its preparation for his later experiments. Since then our manufacture of heparin for research purposes and in a more highly purified form has been continuous. Originally extracted by us almost exclusively from dog livers, heparin in recent years through improvements in technic has been made not only from livers but also from other organs.* The heparin is assayed in this laboratory by Howell's original method on freshly drawn cat's blood, and its physiological antithromboplastic activity is expressed in terms of the number of cubic centimeters of blood which the addition of one milligram of the drug will keep fluid for 24 hours under standardized conditions. Specimens of heparin with a potency as high as

* Due acknowledgment is hereby made of the hearty coöperation in this investigation of our research chemists, Drs. Fitzgerald Dunning, Charles A. Dunning and Wilton C. Harden, and Mr. Arthur E. Stickel.

1 : 200 have thus been prepared, but it has been found for economical reasons and for all practical experimental purposes that a purified heparin of a potency of 1 :50 is quite satisfactory for physiological and pharmacological research. In fact, for a great many routine procedures employed in the clinical laboratories less expensive weaker preparations of heparin (with a potency of 1 : 7.5 or 1.10) have been found entirely adequate.

Influence of Heparin on Toxicity of Ouabain. The powerful cardiac tonic ouabain is generally assayed by determining its lethal dose for cats. A definite concentration is prepared by dissolving a given weight of the glucoside in physiological salt solution and at regular intervals this saline is injected into the femoral vein of a cat under light anesthesia until the heart stops, the respiration continuing for a brief interval thereafter. Such

TABLE I

Assay of Ouabain Solution, 1 : 100,000

M.L.D. of Ouabain Alone	M.L.D. of Ouabain Preceded by Heparin
c.c. per kilo	c.c. per kilo
8.8	11.0
9.8	13.0
9.0	14.0
10.0	15.0
9.0	15.0
8.8	14.0
8.2	20.0
15.5	20.7
10.5	16.5
10.0	12.3
10.5	10.7
11.4	15.6
8.7	11.4
8.5	11.4
9.2	10.3
Average, 9.9 c.c. per kilo	Average, 14.1 c.c. per kilo
P.E. Diff.—0.645	
Critical Ratio—6.5	
σ—1.74	σ—1.03
P.E.—0.32	P.E.—0.56

assays are frequent in this laboratory, the concentration of ouabain employed being usually 1 : 100,000 by weight. When a specimen of ouabain was thus assayed on two series of animals, one of each pair being heparinized 5 to 10 minutes before injection of the drug while the other was employed as usual, the lethal dose for the heparinized cats was generally greater than that obtained from normal control cats. Statistical analysis of the data derived from such sets of experiments demonstrated the validity of difference in the m.l.d. obtained in the two series. Table 1 shows the difference in the m.l.d. of ouabain required for heparinized and non-heparinized cats, respectively. A comparison of the average lethal doses in the two sets reveals that the critical ratio is 6.5, which is far above that required for a valid difference according to statistical criteria.

Influence of Heparin on Toxicity of Digitalis. Results similar to those obtained with ouabain were derived from experiments with tinctures of digitalis. Dilutions of digitalis tincture with physiological saline 1 : 10 were assayed on heparinized and control cats by the Brodie-Hatcher method. The experiments with digitalis and those with ouabain were generally performed in pairs, i.e., one on a normal cat and another on a cat previously heparinized to eliminate variables affecting the toxicity of the digitalis glucosides as, for instance, sudden changes in barometric pressure and other meteorological conditions found to influence the potency in these two sets of cats.[27] Thus in a series of 50 cats, the average lethal dose for the controls was 8.5 c.c., whereas that for the heparinized animals was 10.2 c.c. In control readings σ was 2.63 and P.E., $\pm$ 0.35, and for readings obtained from heparinized animals σ was 2.68 and P.E., $\pm$ 0.36. The P.E. difference between the two series was 0.5 and the critical ratio, 3.4, indicating a statistically significant difference between the results derived from both.

Coagulation Studies on Digitaloid Drugs. To analyze these differences in m.l.d. of ouabain and digitalis for heparinized and non-heparinized animals, studies were made on the coagulation of blood in vitro and in vivo. Samples of blood were obtained from cats under light anesthesia at the beginning of digitalis or ouabain assay and other specimens were drawn from the carotid artery at regular intervals during its progress. It was found that coagulation time of whole blood studied by Howell's method was progressively shortened from beginning to end of the experiment. Similar results were obtained with ouabain. See the subjoined protocols.

Effect of Digitalis Injections in Vivo on Coagulation of Blood

(Experiment of Nov. 28, 1941, on cat, 3.6 kilo., under ether) Assay of 1:10 Dilution of Digitalis: Total injected, 24 c.c.; M.L.D., 6.6 c.c. per kilo.

	Coagulation Time
Normal	8 minutes
After injecting 6 c.c.	6 minutes, 30 seconds
After injecting 10 c.c.	5 minutes, 15 seconds
After injecting 15 c.c.	3 minutes, 45 seconds
After injecting 20 c.c.	1 minute, 45 seconds
After injecting 23 c.c.	1 minute, 15 seconds

Effect of Ouabain Injections in Vivo on Coagulation of Blood

(Experiment of Dec. 19, 1941, on cat, 2.38 kilo., under ether) Assay of Ouabain Sol., 1:100,000—Total injected, 25.5 c.c.; M.L.D., 0.106 mg. per kilo.

	Coagulation Time
Normal	9 minutes, 30 seconds
After injecting 10 c.c.	4 minutes
After injecting 15 c.c.	2 minutes, 40 seconds
After injecting 20 c.c.	1 minute, 40 seconds

A more extensive study was then made of the effect of various digitaloid glucosides on coagulation of shed blood in vitro. Small samples of blood

were mixed with solutions of the different glucosides in varying concentration and their coagulation time was determined. The entire series comprised specimens of digitalin (3), digitalein, digitoxin, digitonin, digilanid, strophanthin (3), ouabain, convallamarin, scillaren and bufagin, the digitaloid principle obtained by Abel and Macht [28] from the toad, *Bufo agua*. All these principles were found definitely to hasten coagulation of blood in vitro.

Control experiments were made with a long series of potent pharmacological agents comprising the glucosides esculin, salicin and phloridzin, the salts of the alkaloids atropine, homatropine and physostigmin, quinine, HCl, quinidine, epinephrine HCl, ephedrine, morphine, codeine, cocaine, spartein, aconitine, crystalline sex hormones, sulfanilamide and other sulfa drugs. The effect of most of these drugs on the coagulation of blood was insignificant. The chief exceptions were epinephrine and crystalline progesterone, both of which tend to shorten coagulation time. The thromboplastic properties of digitaloid drugs are not due to a hemolytic effect because with the exception of two samples of digitalin and of digitonin (a saponin), none produced any hemolysis. The difference in toxicity of digitalis and ouabain for heparinized and control cats can perhaps be ascribed to the thromboplastic properties of the digitaloid principles. To support this view histological studies are being made on hearts of cats used in such tests in hope of detecting microscopic evidence of intravascular clotting.

Experiments with Congo Red. Congo red has long been known as a laboratory reagent for detecting free hydrochloric acid, as a test stain for amyloid and for the estimation of the functional state of the reticulo-endothelial system.[29] Moreover in recent years its use has been extended to therapeutic procedures, and it has been employed empirically with little scientific basis in the treatment of pernicious anemia,[30] pulmonary tuberculosis,[31] purpura hemorrhagica and other conditions. One writer has even recommended it as a chemotherapeutic agent in certain forms of streptococcus septicemia.[32] Serious untoward reactions have occasionally been reported after intravenous use of this drug. Macht, Harden and Grumbein [33] accordingly made a toxicological study of this subject and found that commercial samples of congo red varied much in toxicity and that it was necessary to use a reliably standardized sample for intravenous injection. They found also that the toxicity of this drug for cats was lessened by previous heparinization of the animals. Could this decrease in toxicity be correlated with the effects of congo red on coagulation of the blood? Taliaferro and Haag, who have published an excellent pharmacological study of the dye, reported that injections of small doses of congo red rapidly diminished the coagulation of the blood but when large doses were administered the converse effect was produced and a marked delay in coagulation time was noted.[34] Macht, Harden and Grumbein made similar observations in studies on coagulation of cat's blood in vitro, but Richardson [35] noted no hastening of coagulation after small doses in rabbits. The

results of additional experiments on the toxicity of congo red which the writer made in connection with the present study confirmed his findings. Coagulation time of whole blood obtained from non-heparinized cats during course of administration of congo red was definitely *lessened* after *small injections* but markedly prolonged after large doses. This is illustrated by the following protocol.

Coagulation Experiment No. 1 with Congo Red on Cat Weighing 1.5 Kilo

	Coagulation Time
Normal	7 minutes
After injecting 10 mg. of congo red	4 minutes, 45 seconds
After injecting 10 more mg. of congo red	5 minutes
After injecting 50 mg. of congo red	30 minutes
After injecting 100 mg. of congo red	35 minutes
After injecting 150 mg. of congo red	over one hour

Influence of Heparin on Toxicity of Cobra Venom. Recently introduced into medical practice as a therapeutic agent for the relief of pain, cobra venom is now being used as a substitute for the opiates and other powerful analgesics.[36, 37, 38] Various investigators have, therefore, made extensive toxicological studies of this drug. The principal constituent of cobra venom and that responsible for its analgesic action is a neurotoxin, the chemistry of which is still not completely known, but the latest research on the subject suggests that the cobra neurotoxin is probably of a glucosidal nature.[39] In addition to this active principle, crude cobra venom contains various hemotoxins such as hemolysins, coagulants, agglutinins and precipitins. In general the toxicity of crude cobra venom solutions has proved to be greater than that of solutions of cobra venom, from which proteins and hemotoxins had been removed. The present writer investigated the toxicity of crude cobra venom solutions for cats in conjunction with simultaneous administration of heparin. The average lethal dose of solutions of various lots of cobra venom was first determined on control animals. The same solutions were then assayed on other cats receiving from 5 to 10 mg. of heparin 10 to 15 minutes before injection of cobra venom was begun. In the majority of such experiments prior heparinization of the cats diminished toxicity of the venom. The subjoined kymographic tracings, recording the respiratory movements of two cats treated in this way, illustrate the results obtained. It will be seen that the lethal dose for the control cat was 58.3 c.c. per kilo, whereas that for the cat receiving heparin before injection of cobra venom was 86 c.c. per kilo. Here also, coagulation time varied with the amount of the drug injected.

Anaphylactic Experiments. The effect of heparin on coagulation of blood is not its only interesting physiological property. Other systems affected by heparin than those involved in coagulation have been discovered. Among the most important is the relation of heparin to anaphylactic shock. Divergent reports have been made on the subject. Kyes and Strauser [40] found that heparin injections protected pigeons from shock, and Williams

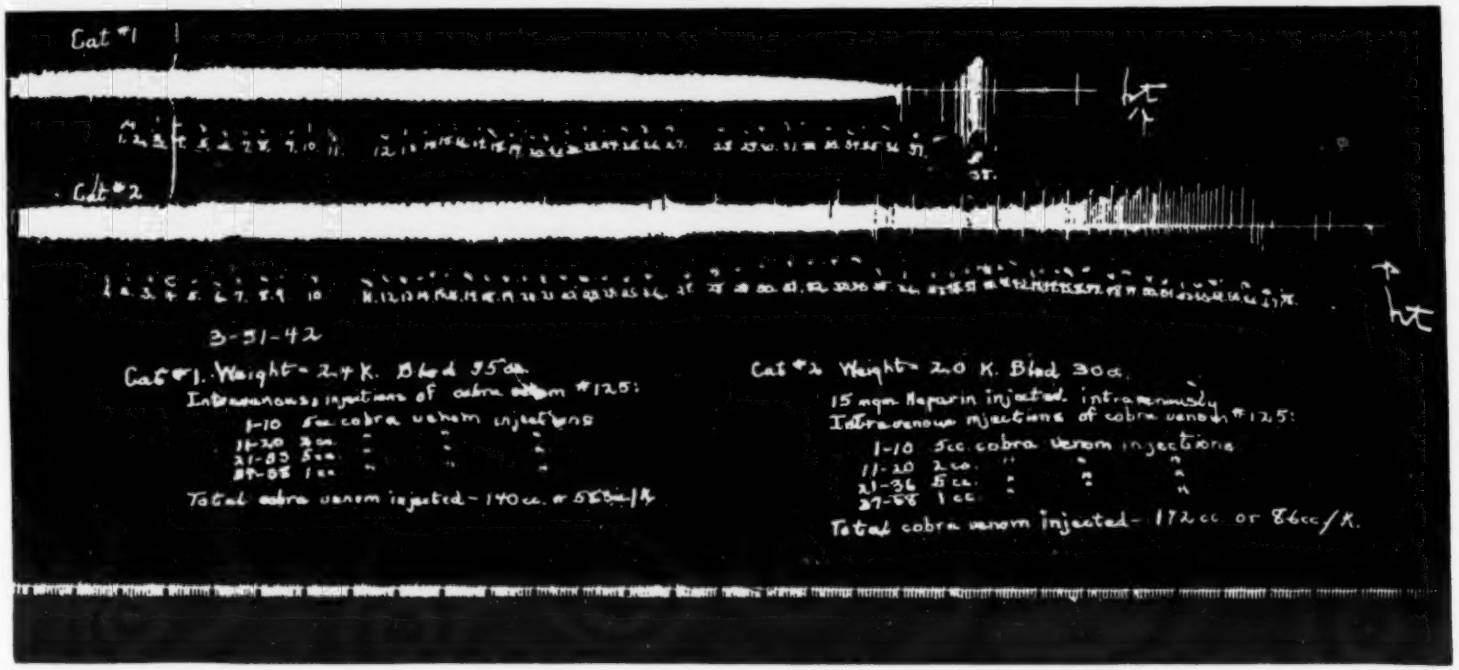

FIG. 2. Effect of repeated injections of crude cobra venom solutions.

Cat 1—Lethal dose, 58.3 c.c. per kilo.
Cat 2—Injection of 15 mg. of very potent heparin was followed by repeated injections of the same cobra venom solution, the lethal dose of which was 86 c.c. per kilo.

and Van de Carr [41] reported similar findings in guinea pigs sensitized with horse serum. A preliminary announcement in 1928 by Macht, Dunning and Stickel [42] also described the protective action of heparin against the shock produced by horse serum in sensitized guinea pigs, rabbits and rats. Hanzlik,[43] Reed and Lamson [44] did not confirm these findings. Repeating his earlier work, the present writer has recently found that guinea pigs can be protected in varying degrees against the anaphylactic shock contingent upon sensitization to horse serum by prior injections of heparin. Table 2 shows the results obtained in such experiments with 50 guinea pigs, 25 heparinized and 25 used as controls. Prior administration of 5 to 10 mg. of heparin solution (1:80) definitely diminished the violence of anaphylactic shock and in some cases prevented such attacks altogether whereas the majority of the controls had severe reactions and died. This corroborative evidence leaves no room for doubt concerning the correlation of heparin effect and anaphylactic shock, at least in some of the lower animals. It was noted that to achieve an antagonizing effect an interval of about 10 minutes must elapse before injection of the antigen. Simultaneous injection of heparin with serum is ineffectual. Closely related to these findings although qualitatively different, are those of other investigators with injections of Witte's peptone in dogs. Wilander [45] found that injections of peptone into the circulation of dogs produced a very severe shock with loss in clotting capacity of blood, and this deficiency, it was assumed, was caused by flooding the blood stream with heparin. Wilander's earlier findings have recently been confirmed by Jaques and Waters,[46] who showed that the anticoagulating substance in blood of dogs in anaphylactic shock is heparin and isolated it in crystalline form from the blood of such animals.

TABLE II

Anaphylaxis in Guinea Pigs

All Animals Sensitized with 0.5 to 1.0 c.c. of Horse Serum. Tests Made Two Weeks Later

Control Guinea Pigs Injected with horse serum alone	Heparinized Animals Injected with 5 to 10 mg. of heparin 10 minutes before horse serum was given
	8 animals developed mild reactions
19 animals—immediate shock, convulsions and death	5 animals developed severe reactions (after 10 to 30 minutes) and died
6 animals developed severe shock but survived	2 developed severe shock and died because serum was injected immediately after heparin
	10 animals developed no reaction and remained well
25—total	25—total

Experiments with Trypsin and Papain. In connection with the experiences of various investigators with heparin in relation to anaphylaxis, the experiments of Rocha e Silva and Dragstedt [47] with trypsin deserve special mention. These authors reported a relation between the liberation of

heparin and administration of trypsin. More recently, these authors together with Wells [48] reported before the Federation of the American Society for Experimental Biology in Boston some further experiences along these lines. They found that injections of trypsin solutions in lightly anesthetized rats are rapidly fatal but that administration of heparin will protect such animals from lethal doses of this drug. The present writer has been conducting similar experiments on guinea pigs and his findings corroborate completely these observations made on rats. A solution of trypsin in physiological saline was injected into the circulation of guinea pigs and the minimal lethal dosage for the animals was determined. The following protocol is a good illustration of such an effect.

Trypsin Experiment of March 25, 1942

Guinea Pig 1, weighing 700 gm., slowly injected intravenously with 5 c.c. of trypsin, 2.5 per cent, in saline.
Died in 35 minutes.
Guinea Pig 2, weighing 600 gm., injected with 10 mg. of heparin (1:100).
Ten minutes later injected with 5 c.c. of trypsin, 2.5 c.c. in saline.
Animal depressed but recovered and lived.

Inasmuch as another proteolytic enzyme, papain, one of vegetable origin, has been described in the older literature [49] as being very toxic on injection in animals and producing anaphylactic shock, other experiments were undertaken by the writer with heparin and papain injections of mice. This investigation is still in progress but the results already in hand seem to point to an antidotal property of heparin against the toxic action of papain, not unlike that encountered in the research with trypsin. Prior injection of heparin into the circulation of mice protected them against lethal doses of the enzyme as may be seen from the following protocol.

Papain Experiment of April 1, 1942

A. Five mice with average wt. of 24 gm., injected in tail vein with 0.5 c.c. of papain solution, 2 per cent. Three out of five mice died within five hours.
B. Five mice with average wt. of 24 gm., injected in tail vein with 5 mg. of heparin, 1:50.
Each injected 10 minutes later with 0.5 c.c. of papain solution.
One mouse died, and four survived.

General Pharmacology. Even the experiments of earlier workers employing crude heparin revealed its low toxicity. At that time a depressant action was found to be exerted chiefly on the blood pressure which fell considerably after injections of the drug into experimental animals. This effect was due to histamine and other impurities mixed with the heparin of that day for later studies with purer products of the drug showed that it was not toxic for the circulatory apparatus with the occasional exception of the blood. Sporadic clinical cases of pathological bleeding have been reported after administration of heparin for therapeutic use. Thus Ershler and

Blaisdell [50] describe hematuria after use of heparin in thrombosis of the cavernous sinus. To the same category belong the recent laboratory findings of Copley and Lalich,[51] who described a hemophilia-like condition in mice after repeated enormous doses of heparin. Strangely enough, these investigators state that the condition they describe was not produced by all brands of heparin they used. Although hemorrhagic tendencies may occur occasionally in patients receiving heparin treatment, such a complication is conspicuous by its rarity,[52] because of the rapid dissipation of the drug's effect after its introduction into the body. Indeed this circumstance is the principal obstacle to the practical application of heparin in the clinic. In this respect heparin contrasts strikingly with some of the newer anticoagulants described in recent medical literature.[53] Yet because of these incidental untoward reactions observed after clinical use of heparin the author decided to study anew its toxicology, especially after administration of large doses of the highly purified product. Experiments were made on the action of heparin on the circulation, the respiration, kidney and liver function, and on the central nervous and neuromuscular systems of cats and rabbits. It was established that the drug affected none either in acute experiments or in animals kept under observation for longer intervals. Figure 3, illustrating the results obtained in such studies on circulation and respiration, shows the effect of a rapid injection of 150 mg. of heparin (1:80) into the femoral vein of an anesthetized cat. Although the amount of heparin injected in such animals was sufficient to keep 12,000 c.c. of cat's blood fluid for 24 hours in vitro, no depressant effect was noted on the respiration and circulation. In fact, other experiments revealed that injections of large doses of heparin occasionally stimulated the vasomotor apparatus, as a small and sustained rise in blood pressure indicated.

Studies conducted on rabbits by the phenolsulphonphthalein method revealed that such large doses of heparin did not impair the kidney function.

The bromsulphalein test also yielded completely negative findings in studies on the liver function of rabbits.

Equally interesting were the results of an investigation of the effect of heparin on the central nervous system and neuromuscular apparatus. Employing a technic used in other researches,[54, 55] the writer studied the behavior of albino rats trained to run in a circular maze after injections of heparin ranging from 1 to 20 mg. had been made in such animals by the intramuscular, intraperitoneal and intravenous routes. It was found that in no case was any depression of the central nervous system or disturbance of neuromuscular coördination produced. Analyses of the numerous data derived from such experiments revealed, on the contrary, a slightly stimulating effect on the running time and behavior of the rats. All the foregoing findings with regard to circulation, respiration, kidney and liver function and the effects of heparin on the central nervous and neuromuscular apparatus speak for a wide margin of safety for this drug.

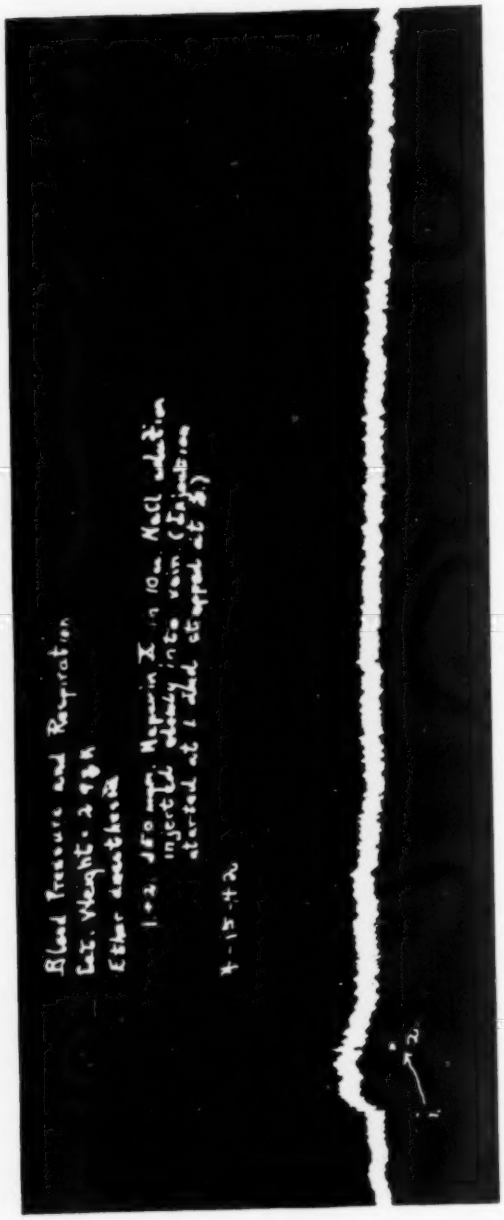

FIG. 3. Cat: 2.9 kilo.—ether anesthesia. Blood pressure and respiratory tracings after 150 mg. of heparin.

Phytopharmacological Studies. The writer has discovered a new property of heparin which is of more general biological interest. It has been the custom in this laboratory when studying the physiological properties of drugs and chemicals to inquire not only into their zoöpharmacological effects on living animals and their tissues but also into their phytopharmacological properties or their effects on living plants.[56] Such studies have been found extremely useful for investigating the biological effects on growth of minute quantities of hormones and vitamins [57]; and phytopharmacological experiments have also been helpful in detecting the presence of certain toxins in the blood of various diseases of man.[58, 59] Experiments were conducted on the growth of *Lupinus albus* seedlings in solutions of heparin in different concentrations, under standard conditions of light, temperature and other ecological factors. It was found that heparin in certain concentrations exerted an auxin-like action on the root growth of *Lupinus albus* seedlings under these conditions. Detailed data on the subject are reserved for publication in a more technical journal of plant physiology. The subjoined data, however, give some idea of the results obtained. Table 3 shows a definite stimulation in growth of seedlings placed in solutions of heparin 1 : 20,000, in plant-physiological saline and allowed to grow in the dark for 24 hours at 20° C. It will be noted that a synthetic homologue of heparin, the sodium salt of polyanethol sulfuric acid, exhibited no such growth-stimulating effect but, on the contrary, produced inhibition of root growth.

TABLE III

Effect of Concentrations of 1 : 20,000 of Heparin on Growth of Lupinus Albus Seedlings at 20° C. for 24 Hours

Brand of Heparin	Index of Growth
H. W. & D., Lot C (1 : 100)	108 per cent
H. W. & D., Lot D (1 : 80)	110 per cent
H. W. & D., Lot E (1 : 100)	109 per cent
H. W. & D., Lot X (1 : 50)	117 per cent
Swedish	108 per cent
Canadian	112 per cent
Swiss	108 per cent
Na polyanethol sulfuric acid	66 per cent

These observations on plants are of interest not only insofar as they confirm the low toxicity of heparin for plants as well as of animals but also in connection with the writer's laboratory experiments, the results of which indicate that heparin solutions in vitro neutralize the toxicity of poisonous substances encountered in the blood of certain diseases. Whether these findings made in the test tube will hold good for clinical trials it is impossible to say now but the writer is investigating this subject in an endeavor to discover if repeated injections of heparin modify to some degree the clinical progress of various pathological conditions.

Keeping Qualities of Heparin. A description of the general pharmacology and toxicology of heparin would be incomplete without a brief ref-

erence to the stability of heparin preparations. Heparin has been found by all investigators to be a stable compound which maintains its potency for a long time. Although highly purified samples kept at room temperature for several months occasionally lose some of their potency, owing probably to some internal change or rearrangement of the molecules, sterile solutions of heparin in hard-glass ampules have been found by us to retain their potency for long periods of time. The author has carried out extensive experiments on the effect of drastic treatment of heparin, in powder form and in solution, with various physical agents and was surprised to find that such exposure effected very little change in the physiological activity of the drug.

TABLE IV

Effect of Physical Agents on Stability of Heparin

1. Heating in autoclave 20 minutes at 15 lbs. pressure	no change
2. Prolonged exposure to sunlight	no change
3. Exposure to polarized light of visible spectrum	no change
4. Irradiation with mercury quartz lamp for one hour	no change
5. Exposure to roentgen-rays, 1000 r	slight weakening
6. Exposure to 1000 gamma ray units of radium emanations	slight deterioration
7. Agitation by high frequency oscillators	no change
8. Extremely high mechanical pressure	no change

The Absorption of Heparin and Duration of Its Effect. The rapid absorption and excretion or disappearance of heparin from the blood stream after injection in lower animals and human beings and the consequent brevity of its anticoagulant effect present the chief obstacle to its wider use in therapeutics. All workers in this field have found that heparin injected in quantities more than sufficient to keep shed blood fluid for many hours outside the body did not retard coagulation time in vivo for more than one hour after administration. In practice it is, therefore, necessary to resort either to frequent injections of this drug or to its administration by slow infusion into a vein by the so-called drip method, trying to the patient and exhausting to the pocketbook. The writer has been studying the absorption of heparin through various portals of entry in an endeavor to find some means of prolonging its anticoagulant effect. The following is a brief summary of the findings made.

Even large doses of pure heparin administered to animals by mouth or stomach tube have no effect on coagulation time of their blood. Local applications of heparin solutions to mucous membranes such as those of the mouth in the sublingual region were also ineffectual in this respect. Small doses, 1 to 5 mg. of heparin (1:100), subcutaneously or intramuscularly injected in rabbits and cats, did not appreciably retard coagulation time. When much larger doses, e.g., 50 mg., were thus given to small rabbits, coagulation time was occasionally delayed in samples of blood drawn 15 to 20 minutes after injection, but not later. Intraperitoneal injections of heavy doses, 50 to 100 mg. of heparin (1:50) were little more effective than injections into the muscle, i.e., slight anticoagulant effect was noted 15 to 30

minutes after its administration, but not later than 45 minutes after. Experiments were also made with suspensions and emulsions of heparin in oil injected into the muscles. These were no more effective than intramuscular injections of aqueous solutions. Implantation in experimental animals of pellets containing heparin covered with a protective substance had no effect as far as prolongation of its anticoagulant action was concerned.

It has, therefore, hitherto been the practice of all investigators to resort to intravenous injections for the study of heparin in both experimental and therapeutic cases. Unfortunately even massive doses of the drug thus injected into the vein in the author's experience have been found to exert their greatest potency only within a limited period of time. The most powerful anticoagulant effect after such injections occurred from 10 to 30 minutes after injection and in the majority of experiments on cats and rabbits the

Duration of Effect of Heparin Administered to Rabbits by Various Routes

Rabbit A, weighing 2 kilo.
October 21, 1941—Normal coagulation time—9 min., 20 sec.
Injected 5 mg. of heparin (1:50) in muscles of leg
After 20 minutes, coagulation time—9 min., 15 sec.
After 35 minutes, coagulation time—9 min., 10 sec.
After one hour, coagulation time —9 min.

Rabbit B, weighing 2.5 kilo.
October 21, 1941. Normal coagulation time—8 min., 25 sec.
Injected 5 mg. of heparin (1:50) into ear vein
After 30 minutes, coagulation time—12 minutes, 5 sec.
After one hour, coagulation time — 2 minutes

Cat No. 5, weighing 3.0 kilo.
April 6, 1942—normal coagulation time—10 minutes
2:58 p.m., injected in vein 10 mg. of heparin (1:80)
3:08 p.m., coagulation time ..... 57 minutes
3:24 p.m., coagulation time ..... 37 minutes
3:46 p.m., coagulation time ..... 23 minutes
3:59 p.m., coagulation time ..... 17 minutes
4:11 p.m., coagulation time ..... 11 minutes
4:18 p.m., coagulation time ..... 9 minutes

anticoagulant effect vanished within an hour after administration of the drug and was usually superseded by a compensatory rebound or shortening of the coagulation time as compared with the normal. The protocols exemplify the usual results obtained in cats and rabbits after intramuscular and intravenous injections of the drug.

The Absorption of Heparin through Bone Marrow. How to prolong the typical antithromboplastic effects of heparin is still an unsolved problem, but results of experiments recently carried out in this laboratory point to another approach to solution of this riddle. Within the past few years diverse reports have appeared in the medical literature concerning the transfusion of blood and plasma through the bone marrow. The brilliant work

of Morrison and Samwick,[60] and of Tocantins[61] and O'Neill,[62] is especially noteworthy in this connection. The former investigators have successfully injected blood and bone marrow cells into the marrow of various patients, and the latter have developed a satisfactory technic of transfusing plasma, glucose solutions and whole blood in animals and human beings by a similar route.

The present writer for many years has been engaged in a study of the absorption of drugs and poisons through various portals of entry into the body.[63] In this connection it was found that aqueous solutions were readily absorbed through the bone marrow and thus produced their characteristic pharmacodynamic effects.[64] Of special interest in this connection, however, were the findings made with different kinds of oils. The so-called essential or volatile oils are rapidly absorbed when injected into the medullary cavity of long bones and produce depression of the nervous system, convulsions, coma and death, depending on the dose injected. The fixed oils, such as olive oil, sesame oil, peanut oil, cottonseed oil, when injected into the bone cavities, acted very differently. No toxic effect was noted after injection of such oil and it was surprising to find that no fat or oil embolism occurred in experimental animals. It was further found that when active pharmacological principles, such as epinephrine, were suspended in a fixed oil like olive oil and introduced into the tibia of a rabbit, cat or dog, the absorption of the epinephrine was very slow, the result being a characteristic rise in blood pressure which was sustained for a long time, 35 to 45 minutes, a result quite

Rabbit D, weighing 2.5 kilo.

October 21, 1941. Normal coagulation time—9 min., 20 sec.

Injected 5 mg. of heparin (1:50) suspended in 0.8 c.c. of olive oil into cavity of right tibia

After 25 minutes, coagulation time—24 minutes

After 50 minutes, coagulation time—11 minutes

After one hour and 40 minutes, coagulation time—14 minutes.

Cat No. 6, weighing 2.0 kilo.

April 7, 1942. Normal coagulation time—5 min.

2:31 p.m., injected 2 mg. of heparin, lot No. 10 (1:80), dissolved in 0.4 c.c. of saline in cavity of right tibia

2:32 p.m., injected 4 mg. of heparin, lot No. 10 (1:80), suspended in 0.6 c.c. of olive oil into cavity of right tibia

2:45 p.m., coagulation time	21 minutes
3:03 p.m., coagulation time	9 minutes
3:17 p.m., coagulation time	20 minutes
3:33 p.m., coagulation time	22 minutes
3:48 p.m., coagulation time	12 minutes
4:03 p.m., coagulation time	12 minutes
4:18 p.m., coagulation time	12 minutes
4:30 p.m., coagulation time	12 minutes
4:50 p.m., coagulation time	12 minutes
5:00 p.m., coagulation time	12 minutes
5:10 p.m., coagulation time	12 minutes

unlike that obtained by intramedullary injections of the same drug in aqueous solutions. These experiments suggested a similar technic for the study of heparin with the object of prolonging its antithromboplastic effect. Suspensions and emulsions of pure heparin were made in olive oil and small quantities of these were slowly introduced into the tibia and other long bones. It was found that such a procedure effected a slow absorption of heparin and extended its anticoagulant action for a much longer time than did intravenous injection of the drug. Numerous control experiments with injections of olive oil and other fixed oils in small quantities revealed that such injection of oils into the bone cavities were usually not injurious and fat embolism occurred only in rare and exceptional instances. The heavy oil employed in the animal experiments appeared in some way to retard the absorption of heparin and acted as a reservoir releasing the drug in small quantities into the circulation and ensuring its action for a much longer time than it could be maintained after intramedullary administration of aqueous solutions of the anticoagulant. The protocols are a typical illustration of the results obtained.

Comment

In addition to its hormone-like regulation of blood coagulation, heparin possesses other pharmacological properties of considerable interest. The decrease in toxicity of ouabain and digitalis for heparinized cats, as compared with normal animals, and similar findings regarding lethal dosage of cobra venom and congo red may or may not be correlated with their antithromboplastic property. The present writer's observations on the effects of digitaloid glucosides, cobra venom and congo red on coagulation, however, certainly lend some support to this view. Moreover these findings suggest that a tendency to intravascular clotting and a predisposition to thrombo-embolic accidents in certain pathological conditions or in the course of administration of certain drugs may be of commoner occurrence than hitherto suspected. Poisons of endogenous or exogenous nature may be responsible for precipitating such catastrophes and when such a contingency threatens, administration of heparin may be considered as a rational prophylactic measure. The complexity of the subject is shown also by the recent observations of Winternitz and his coworkers, who studied the effects on blood pressure and circulation of injections of various tissue extracts with and without heparin and noted divergent results in two series of experiments.[65]

Equally interesting is the antagonistic action of heparin for certain forms of anaphylactic shock. Here again, that phenomenon in some obscure fashion may be correlated with anticoagulative properties of the drug. Such a hypothesis may warrant a clinical trial of heparin as a prophylactic measure to mitigate the severe reactions liable to follow injections of various sera and vaccines. Certainly the low toxicity of heparin, which is reported in this paper, and shown by extensive previous observations of fellow work-

ers, renders such a prophylactic procedure harmless and supports the view that heparin is a hormone-like normal product of the animal metabolism continually secreted or elaborated for maintenance of normal physiological functions of the blood.

The low toxicity of heparin for animals and plants appears to warrant its more liberal employment in a clinic. More puzzling, however, are the great stability and resistance of heparin to physical agents, on the one hand, in contrast to its rapid absorption and equally rapid disappearance in the body, on the other. How to prolong the duration of its anticoagulant action more satisfactorily than by intravenous injection is a problem still unsolved, although the results of experiments on animals with intramedullary administration of oily suspensions and emulsions of the drug are very suggestive in this connection. It is astounding to learn, as in the present writer's experience, that oil or fat embolism, hitherto the nightmare of the experimental pathologist, is but a rare occurrence so far as serious or even mild injury to lower animals is concerned after intramedullary injection of fixed or heavy oils. Nevertheless, it would be hazardous to conclude that the data yielded by tests on rabbits and cats may be transferred per se to the practice of human therapeutics.

Summary

1. Specimens of purified heparin of high potency are remarkably resistant to acute treatment with physical agents, heat, ultraviolet rays, roentgen-rays, radium emanations and various mechanical manipulations.

2. Heparinization of cats prior to intravenous injections of ouabain and digitalis solutions significantly lowers the toxicity of these drugs. This difference in toxicity is probably correlated with a thromboplastic effect of digitaloid glucosides observed in vitro.

3. The toxicity for cats of cobra venom and congo red, intravenously injected, is also diminished by prior heparinization of the animals.

4. Large doses of heparin injected into guinea pigs sensitized with horse serum tend to prevent anaphylactic shock or to reduce its violence.

5. Massive doses of pure heparin have no toxic effect on the circulation and respiration, the kidney and liver function, the central nervous system or the neuromuscular behavior of animals.

6. Aqueous solutions of heparin in concentrations of 1:20,000 to 1:80,000 exert a stimulating or auxin-like effect on root growth of *Lupinus albus* seedlings reared under standardized plant-physiological conditions.

7. The anticoagulant effect of heparin on intramuscular or intraperitoneal injection is inconstant and negligible. Intravenous injections of the drug usually exert an antithromboplastic effect for not more than one hour after administration. Intramedullary injection of cats and rabbits with heparin suspended in fixed oils or emulsions prolongs its anticoagulant action.

8. All of these findings, obtained in laboratory experiments on animals and plants, must not be regarded per se as applicable without reservation to human therapeutics. However, they serve as a starting-point or stimulus for further physiological and pharmacological research on the subject and give some hint of eventual usefulness in medical practice.

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SUGAR ALCOHOLS XXIV. THE METABOLISM OF SORBITOL IN DIABETES *

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Sorbitol was introduced into therapeutics in Europe under the name of "Sionin" by Thannhauser and Meyer [1] in 1929. Since that time various workers have investigated its value as a substitute for carbohydrate in the diabetic diet with no consistent findings. Reinwein [2] administered sorbitol to diabetics and observed an increase in the respiratory quotient but no rise in blood sugar. On the other hand, Roche and Raybaud [3] observed no increase in the respiratory quotient, and Donhoffer and Donhoffer [4] reported a rise in blood sugar after giving sorbitol to diabetic patients.

Kaufmann [5] reported that sorbitol exhibited a protein-sparing action and was useful to the diabetic. Gottschalk [6] ascribed an "insulin-enticing" action to this compound and recommended its use in diabetics. von Noorden [7] also recommended the use of sorbitol in the diet of mild and moderately severe diabetics. Excellent utilization of sorbitol was observed by Bertrand, Radais and Labbé [8] in diabetic patients with and without insulin.

In 1933 Payne, Lawrence and McCance [9] reported that sorbitol was not directly metabolized and was an inert compound which could be used safely as a sweetening agent by diabetics. Raybaud and Roche [10] reported that sorbitol was not a satisfactory substitute carbohydrate and questioned its value in diabetes. In this country Silver and Reiner [11] reported that sorbitol produced hyperglycemia in a diabetic patient.

Recently in this country sorbitol has been made available at a comparatively low cost and its possible continued use as an item of diet in normal individuals has received much attention.

Ellis and Krantz [12] observed that 25 or 50 gm. of sorbitol increased the respiratory quotient of normal individuals as much as an equal amount of dextrose. At the same time, sorbitol did not significantly elevate the blood sugar.

The present investigation is concerned with the effects of sorbitol on the respiratory quotient and the blood-sugar level in mild and moderately severe diabetics.

Experimental. Thirteen patients were made available for this study by the staff of the University Hospital. Details of the conditions under which this work was done were similar to those previously described.[12] In each experiment 50 gm. of dextrose or sorbitol were given orally to the patient

* Received for publication June 10, 1942.
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The expense of this work was defrayed in part by a grant from the Atlas Powder Company of Wilmington, Delaware.

TABLE I

Patient	Time	50 Gm. Dextrose		50 Gm. Sorbitol	
		Blood Sugar mg. per cent	Respiratory Quotient	Blood Sugar mg. per cent	Respiratory Quotient
N. B.	Fast.	153	0.75	152	0.70
	½ hr.	180	0.75	167	0.75
	1 hr.	221	0.78	165	0.75
	2 hrs.	232	0.79	156	0.73
A. D.	Fast.	140	0.80	154	0.75
	½ hr.	194	0.77	167	0.76
	1 hr.	222	0.79	180	0.80
	2 hrs.	235	0.87	151	0.80
H. R.	Fast.	157	0.76	181	0.70
	½ hr.	190	0.72	173	0.70
	1 hr.	190	0.71	166	0.73
	2 hrs.	211	0.77	166	0.74
J. L.	Fast.	153	0.68	169	0.70
	½ hr.	178	0.67	173	0.70
	1 hr.	200	0.73	175	0.72
	2 hrs.	189	0.80	166	0.72
K. T.	Fast.	256	0.70	227	0.70
	½ hr.	308	0.69	227	0.70
	1 hr.	312	0.74	223	0.65
	2 hrs.	308	0.77	225	0.71
I. E.	Fast.	136	0.70	133	0.72
	½ hr.	164	0.70	140	0.74
	1 hr.	189	0.70	143	0.76
	2 hrs.	200	0.74	143	0.75
L. M.	Fast.	140	0.73	138	0.70
	½ hr.	224	0.71	136	0.72
	1 hr.	222	0.70	133	0.72
	2 hrs.	222	0.75	135	0.70
M. P.	Fast.	163	0.63	146	0.64
	½ hr.	224	0.64	151	0.71
	1 hr.	244	0.62	148	0.72
	2 hrs.	225	0.66	141	0.71
R. M.	Fast.	122	0.71	125	0.73
	½ hr.	140	0.73	121	0.77
	1 hr.	170	0.76	120	0.75
	2 hrs.	190	0.79	120	0.76
C. B.	Fast.	143	0.71	133	0.66
	½ hr.	174	0.76	143	0.68
	1 hr.	200	0.74	133	0.76
	2 hrs.	222	0.76	133	0.75
D. S.	Fast.	133	0.73	143	0.83
	½ hr.	161	0.70	121	0.80
	1 hr.	134	0.77	123	0.80
	2 hrs.	120	0.87	110	0.75
A. E.	Fast.	136	0.68	156	0.64
	½ hr.	200	0.70	158	0.66
	1 hr.	235	0.74	154	0.68
	2 hrs.	250	0.77	151	0.67
T. S.	Fast.	116	0.64	114	0.65
	½ hr.	157	0.71	126	0.66
	1 hr.	172	0.78	133	0.65
	2 hrs.	162	0.78	135	0.70

and the influence of the two compounds on the blood sugar and respiratory quotient was compared.

The results of individual experiments are shown in table 1 and the average values are shown graphically in chart 1.

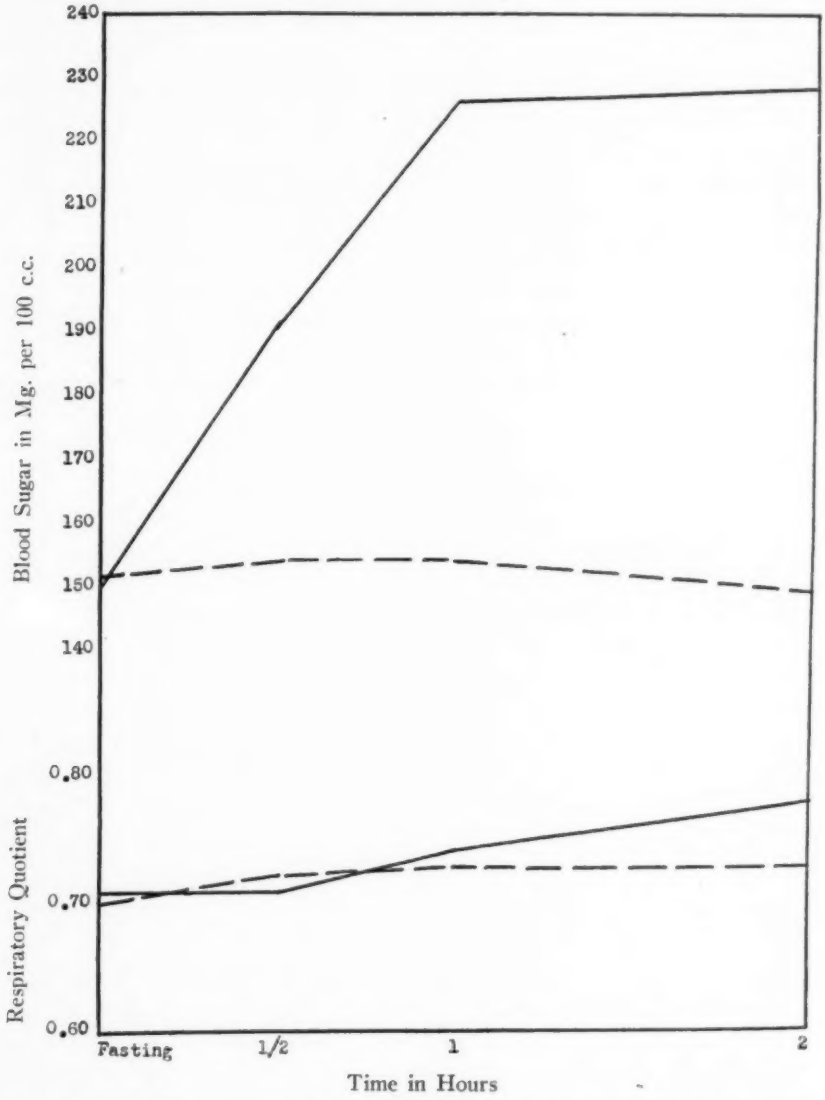

CHART 1. Influence of dextrose and sorbitol on the blood sugar and respiratory quotient of diabetics. Average of 13 cases. Solid line, dextrose; broken line, sorbitol.

DISCUSSION

It was shown previously that sorbitol significantly elevates the respiratory quotient of normal individuals when ingested in 25 and 50 gm. quantities.

This occurs without a concomitant hyperglycemia. If these phenomena occurred in the diabetic it would strongly indicate utilization without drain on the impaired insulin stores. However, in the rat and *Rhesus macacus* monkey sorbitol serves as a precursor of hepatic glycogen and in all probability the same metabolic pattern obtains in man. It is obvious from an examination of chart 1 that sorbitol does not significantly raise the respiratory quotient of the diabetic. This strongly suggests the improbability of its direct utilization in the diabetic. In the liver sorbitol is converted to levulose [13] and polymerized into glycogen. It would follow, therefore, that when glycogenolysis occurs providing for glucose utilization in the periphery, insulin would be required for its catabolism. Thus after depolymerization of glycogen, of which sorbitol is a precursor, the fate of glucose and sorbitol in the body is likely identical, each requiring insulin. This in turn bespeaks that its use in diabetes must be in accordance with the patient's residual tolerance for glucose or his insulin dosage. Whether glucose and sorbitol, gram for gram, require the same or different amounts of insulin for their utilization has not yet been determined. This problem is still under investigation in this laboratory in depancreatized dogs.

There remains, however, another consideration in the use of sorbitol in the diabetic diet. When ingested, sorbitol produces no significant postprandial hyperglycemia. As it is absorbed from the alimentary tract there is, however, a likelihood of a high blood-sorbitol level. As sorbitol is a nonreducing carbohydrate-like substance (sugar alcohol) its presence in the blood is not made manifest by the usual methods of determining blood-sugar. The absorbed sorbitol is oxidized to levulose, polymerized to glycogen and depolymerized to glucose. These conversions are orderly time reactions and prevent a plethora of glucose from appearing in the blood, which occurs immediately after the ingestion of the latter. Undoubtedly the absence of a precipitous hyperglycemia from the regimen of the diabetic exerts a benign influence on his carbohydrate tolerance, for large quantities of carbohydrates fed to partially depancreatized dogs cause characteristic lesions (hydropic degeneration) in the β cells of the islet tissue and in the diabetic reduce further the carbohydrate tolerance. The relative effects on the impaired islet tissue of a hyperglycemia and a high blood-sorbitol level, to our knowledge, have not yet been investigated. We consider this an important phase of this question of the ultimate advantage or danger of sorbitol in the diabetic, and as yet it remains unanswered.

Summary

In 13 mild and moderately severe diabetic patients sorbitol failed to influence significantly either the blood-sugar level or the respiratory quotient. Its place in the diabetic diet has been discussed.

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MÉNIÈRE'S SYNDROME AND MIGRAINE: OBSERVATIONS ON A COMMON CAUSAL RELATIONSHIP *

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THE possibility of a relationship between migraine and the syndrome known as Ménière's was suggested by Ménière himself in his original paper. Although later observers have also seen the possibility, only recently has any satisfactory basis been established for the mechanism of either, so that hitherto the theory of a relationship has had to depend upon clinical observation and conjecture rather than upon the result of experiment. It has been probability rather than fact. The object of this paper is to attempt to show that the two conditions have an actual causal relationship, the basis of both being a vascular dysfunction.

Definition. When conditions so polymorphic as paroxysmal headache and paroxysmal vertigo are to be studied, it is essential that a clear-cut definition of the class of case under consideration be given. When the two are to be compared this desideratum is even more important. It has been in part the failure to do this which has led in the past to the diversity of opinion and therapeutic claim in the case of both conditions. O'Sullivan [10] has brought out this point very effectively in her migraine studies.

The definition of migraine given by Brain [3] is of "a paroxysmal disorder characterised in its fully developed form by visual hallucinations and other disturbances of cerebral function, associated with unilateral headache and vomiting." Migraine, however, is a condition which shades off from the fully developed form into a great number of lesser variants, so that by some observers almost any periodic headache will be accepted as migraine. In this paper a somewhat less rigid definition than that quoted will be adopted, though one with very definite limits. It is proposed to accept as migraine cases of severe paroxysmal unilateral headache associated with gastrointestinal disturbances, arising at puberty or soon after and persisting until middle life or later, but it will not be insisted that there should *necessarily* be disturbances of cerebral function to establish the diagnosis. Only cases conforming strictly to this pattern will be called migraine.

Similarly with Ménière's syndrome, variations in severity of symptoms and in the chronology of their appearance are common. Vertigo may be mild and may at times precede deafness and tinnitus by months and even years. For the purpose of this paper, however, only those cases have been acceptable which have shown the complete classical syndrome of severe attacks of paroxysmal vertigo associated with increasing deafness and tinnitus.

Such self-denying ordinances, although they limit the material available,

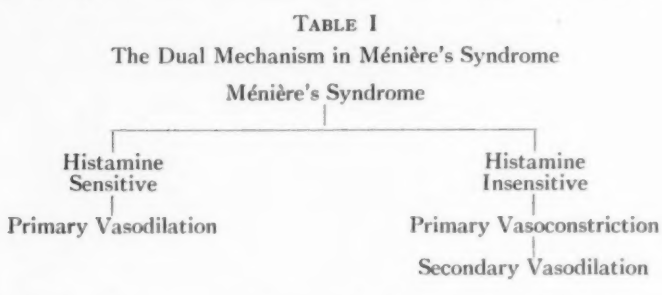
* Received for publication August 1, 1942.
Read before the Section of Neurology and Psychiatry at the Annual Meeting of the American Medical Association, Atlantic City, June, 1942.

are essential to the establishment of the thesis. Only when this has been achieved will it be permissible to relax definition.

The Mechanism of Ménière's Syndrome. (Table 1.) It has been shown, it is believed satisfactorily, that cases of Ménière's syndrome can be divided into two groups by means of an intradermal test with histamine (Atkinson [2]).

TABLE I

The Dual Mechanism in Ménière's Syndrome



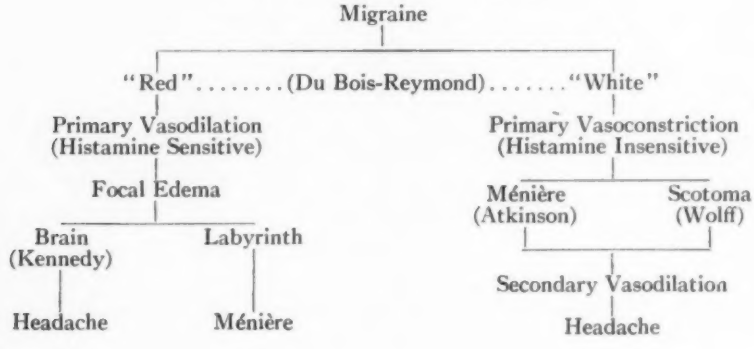
(1) First there is a small group which is sensitive to histamine, which has a primary vasodilator or, more orthodoxly, an allergic basis, and which can be satisfactorily treated by desensitization to histamine or by elimination of the specific antigen when such can be discovered.

(2) There is a second group, the large majority, which is insensitive to histamine, and in which the attacks are the result of a primary vasospasm. Cases in this group can be relieved, in the great majority of cases, by the exhibition of vasodilator drugs, of which the most satisfactory in the writer's hands has proved to be nicotinic acid. This advocacy of a particular drug, however, is not intended to imply that vasospasm is due to one single factor, any more than that the manifestations of allergy are produced by one single antigen. The precipitating factors of vasospasm are probably many, but concern at the moment is not with them. What is of concern here is the principle, the vasospasm.

The Mechanism of Migraine. (Table 2.) In this condition also there is evidence of a dual etiology, of the same nature as that which applies in Ménière's syndrome.

TABLE II

The Dual Mechanism in Migraine



(1) The thesis of allergy as a cause of migraine attacks was put forward and upheld by Kennedy,[6] and has been very generally accepted as applying correctly at least to a portion of the cases.

(2) On the other hand, Wolff and his collaborators [11] have shown that migraine attacks can be the result of a primary vasospastic process, that the preliminary visual disturbances are vasospastic in origin and can be abolished by the inhalation of amyl nitrite in small doses, and that the headache itself is the result of a secondary compensatory vasodilation. This accords in all respects with the writer's findings in the second, or histamine insensitive, group of Ménière cases.

These two groups correspond with the "red" and "white" migraine of du Bois Reymond, a classification which has been commonly decried in recent years but which appears increasingly to have validity.

Association of the Migraine Syndrome with Ménière's Syndrome. What it is sought to establish, however, is not only an identical mechanistic basis but an actual etiological relationship, a relationship like that which joins, for instance, all pneumococcal manifestations together into one family by virtue of their dependence upon a specific organism, as against the broader tie of bacterial diseases in general. For this there is clinical evidence.

Headache not uncommonly accompanies or is associated with Ménière attacks. Mygind and Dederding [9] found the association in 19 per cent of their cases, but did not define the type of headache they referred to. I have found headache in general to be a much more usual accompaniment of Ménière's syndrome. In some form or another it has been present in 63 out of 108 cases, just over 58 per cent. Twenty-two of these could be classed as clear-cut migraine, or 20 per cent of all cases, a figure practically the same as that of Mygind and Dederding. Moreover, the laterality of the headache, or its predominant laterality in cases not invariably on the same side, has in every instance been the same as that of the deaf or deafer ear. Finally, migraine, migraine strictly according to the letter of the law, has been found to occur in both groups of Ménière cases (tables 3 and 4).

TABLE III

Numbers in Present Series

Total Ménière Cases	108
Vasodilator Group	20
Vasoconstrictor Group	88
Cases with Migraine	22
Vasodilator Group	10
Vasoconstrictor Group	12
Cases with Non-Specific Headache	42
Vasodilator Group	6
Vasoconstrictor Group	36
Cases without Headache	44

The Vasodilator (Allergic) Group. Twenty cases of Ménière's syndrome have fallen into this group, and 10 of these (50 per cent) have also

TABLE IV
Ménière Cases Associated with Migraine
Results of Treatment on Headache

	No Treatment	No Change	Improved	Relieved
Vasodilator Group, 10	5	0	1	4
Vasoconstrictor Group, 12	5	0	4	3

suffered from migraine. Of the 10, four were not treated for their allergy, three not returning to Clinic and being untraceable, the other having an operation for eighth nerve section which relieved her dizziness though other symptoms, among them headache, continued to be severe and disabling; and in a fifth case the migraine attacks had ceased some years before she was seen on account of vertigo. The remaining five have been treated by desensitization to histamine as described elsewhere.[2] In four instances the migraine attacks have been abolished coincidently with the Ménière attacks; in the fifth case the migraine has been considerably improved both as regards frequency and severity, and the Ménière manifestations have ceased.

The Vasoconstrictor Group. Of 88 Ménière cases in this group, 12 have had classical migraine (13.6 per cent). In five cases the migraine had ceased before or coincidently with the onset of Ménière attacks. The seven remaining cases in which migraine attacks still occurred have been treated for their Ménière's syndrome without regard to their migraine, in the manner described elsewhere [2] for cases of the vasoconstrictor group, with nicotinic acid. In all seven, vertigo has been relieved over periods varying from 18 months in the oldest case to six months in the most recent, and in all cases for periods considerably longer than previous intermissions. At the same time their migraine has been improved; in the case of four very considerably, three of them so much that they have maintained that they are well of it though admitting that they still have an occasional mild headache; and three have been relieved entirely of headache for periods (as of December, 1941) of 8, 12, and 15 months.

The Chronology of Migraine Headache in Relation to Ménière Attacks. There is an interesting and characteristic difference in the timing of the headache in relation to the vertigo in the two groups.

1. Vasodilator (Allergic) Group. In the smaller group of histamine sensitive patients, the headache *precedes* the vertigo and serves in some sort as an aura. It may start as many as 24 hours before and is, at any rate at first, unilateral on the side of the deafer ear. Gradually it increases in intensity until it becomes an intense, bursting pain of great severity which, when it reaches its height, explodes like a rocket in a dizzy attack. For a few moments vertigo is extreme, then it gradually subsides and disappears leaving behind only an aftermath of unsteadiness. At the height of the attack the patient usually vomits, then feels completely exhausted and finally

falls into deep sleep from which he awakes more or less recovered. Such an episode might be called with equal justification a migraine attack with vertigo or a Ménière attack with headache.

2. Vasoconstrictor Group. In the much larger group of histamine insensitive patients, the headache *succeeds* the vertigo instead of preceding it as in the previous group. With little or no warning, the patient is seized with vertigo of considerable severity, even severe enough to knock him down, and in the cases under discussion this is immediately followed by a headache having the characteristics of migraine. The sequence is vertigo followed by unilateral headache on the deaf side, nausea and perhaps vomiting, rapid relief of extreme vertigo, gradual relief of headache. Evidently here the vertigo of a Ménière attack is the equivalent of the visual disturbances of migraine.

In both groups, but especially in the vasoconstrictor group, either symptom may occur on occasions without the other—headache without vertigo, vertigo without headache. Presumably on these occasions the vasospasm is more restricted in its area of impact.

Scotoma and Vertigo. It appears, then, that the scotoma of migraine and the vertigo of Ménière are the result of the same mechanism, a vasospasm of cerebral vessels acting in different situations. Moreover, the disparity between these two situations is not in fact so wide as it seems at first if the origin of the vascular supply rather than its termination is considered. The auditory artery which supplies the labyrinth is a branch of the basilar artery, the posterior cerebral which supplies the occipital lobe is its terminal branch. Thus a migraine headache may follow a labyrinthine disturbance just as well as a visual disturbance, and vertigo can take the place of scotoma as the pre-headache phase of an attack which in the one instance is called Ménière and in the other migraine.

Furthermore, just as vertigo often occurs without succeeding headache in Ménière's syndrome, so scotomata may occur without succeeding headache in the later years of a migraine history (Case 3). Occasionally even a scotoma may arise without headache having ever been a symptom, though other manifestations of a migraine diathesis are present (Case 4). Such cases are apt to be a puzzle unless they are recognized for what they are, a part of the migraine syndrome. They have the same mechanism as the scotomata of migraine, the vertigo of Ménière—vasoconstriction; and they can be relieved by measures directed to overcoming it.

Conversion of Migraine Syndrome into Ménière's Syndrome. In yet other instances, one manifestation leads to the other—the "sick headache" of youth turns into the Ménière attack of middle age (Case 2). This was the case in five instances in this series, all belonging to the vasoconstrictor group. Sometimes there is an interval between the two of several years; sometimes the Ménière attacks follow immediately upon the cessation of the migraine. "My headaches stopped when my dizzy attacks started" (251542, Clinic). Moreover, these patients commonly do not have the complete syn-

drome. Their migraine in the past may not have been preceded by visual disturbances; and later their Ménière attacks are not necessarily directly associated with headache, though unassociated headache without all the migraine characteristics is frequent.

A reasonable explanation seems to be that in the years of youth the vasospasm is minimal, producing inconspicuous symptoms or none at all, though these patients can sometimes recall, especially if specifically questioned, occasional blurring of vision or occasional mild dizziness in attacks in earlier years, minor matters which were disregarded in the severity of the headaches. The succeeding relaxation, however, the youthful rebound, as it were, is maximal and produces the characteristic headache. As time goes on, and age, combined no doubt with the effect of repeated insult, diminishes the resilience of the vessels, the secondary vasodilation which used to produce the headache ceases to occur. All that happens now is the spasm, but that the more effectively because of the lessened vascular elasticity.

Migraine and Hypertension. It is an old clinical observation that migraine patients tend to "grow out of" their headaches, which presumably means that at least their secondary dilation gradually ceases to occur. It is now coming to be recognized that they may also "grow into" something else. There are the five cases already mentioned here in which migraine has given way to Ménière attacks. A parallel observation of the merging and changing of migraine into another condition with age has been made by Gardiner and his associates,[5] who have shown that migraine sufferers in youth tend to become hypertensives with age. The observation fits in with the hypothesis put forward here. It must be admitted, however, that patients with Ménière's syndrome are not necessarily, nor indeed usually, afflicted with hypertension. Indeed, contrary to the popular view, among the older patients in the presumably degenerative group a high blood pressure is the exception rather than the rule. Perhaps hypertension involves among other things a stiff, unyielding vascular tree which prevents the degree of both contraction and relaxation necessary for a paroxysmal attack, so that a patient with the migraine diathesis may develop hypertension or Ménière attacks, but not both. This, if it is so, is a beneficent dispensation of Providence, for to have both would be too much.

"Formes Frustes." In order to forestall criticism, a very rigid criterion of diagnosis has been adopted for the purpose of this paper. But in practice many cases of headache with Ménière attacks occur which, though they do not comply absolutely with this definition of migraine, nevertheless might be and usually are accepted by the clinician as minor variants or "formes frustes." For instance, many Ménière cases complain of periodic headache not clear-cut enough to be labeled classical migraine (table 3) yet often mainly unilateral and on the side of the deafer ear, and it is remarkable how frequently the headache in these cases clears up with the institution of treatment directed towards the Ménière attacks. Many patients say very early in treatment that, whereas their vertigo has been diminished

though not yet abolished, the main improvement they notice is in their headaches which have disappeared. On the other hand, there are also many cases of undeniable migraine who complain of some degree of dizziness yet who are not acceptable as Ménière cases because they do not have the complete syndrome. Some of these patients actually show in an audiogram an early cochlear involvement on the affected side of which they are quite unaware (figure 1).

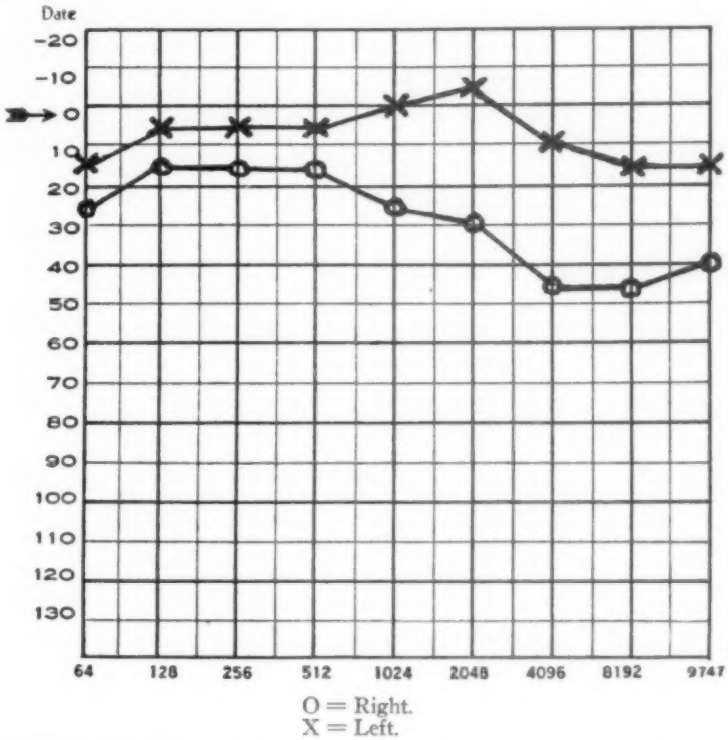


FIG. 1. Audiogram from case of a woman of 37 who had suffered from right-sided migraine since childhood and who was unaware of impaired hearing on that side.

It is in these intermediate cases that confusion of diagnosis occurs. When headache predominates such patients tend to be seen by the neurologist and to be called migraine; when vertigo predominates they tend to be seen by the otologist and to be called Ménière's disease; when both symptoms are present, the two fight over the body. Actually if the thesis put forward here is accepted, whether headache or vertigo predominates matters not at all. The fundamental process is the same; only the locale differs. Etiologically speaking, Ménière's syndrome is aural migraine.

Therapeutic Response. As important a piece of evidence as any is that of therapeutic response. All these patients have been treated as for Ménière's syndrome by methods which have already been described elsewhere.[2] No special therapeutic attention has been paid to their headaches,

yet the results as regard headache have been as satisfactory and as lasting as have the results as regard vertigo (table 4). In the vasodilator or allergy group, desensitization has relieved headache and vertigo together. In the vasoconstrictor group weekly headaches which previously had been relieved by ergotamine temporarily have been relieved for many months following the use of nicotinic acid combined with conventional general measures. And this is not surprising when the primary vasoconstrictor mechanism of migraine is borne in mind. Ergotamine in therapeutic doses is a vasoconstrictor drug, and relieves headache by overcoming the secondary vasodilation which produces it. It does nothing to prevent its recurrence. Nicotinic acid, as a vasodilator, attacks the basic process, vasoconstriction. It goes to the root of the matter; by preventing the primary phase it also prevents the secondary. Moreover a number of cases which do not conform to the strict definition demanded here, cases of migraine without vertigo or of atypical headache with vertigo, have given satisfactory results with treatment on the same lines. They lend a certain collateral support to the thesis.

It must again be insisted here, as I have already insisted elsewhere [2] in considering Ménière's syndrome alone, that the advocacy of nicotinic acid for treatment is not meant to imply that these conditions are vitamin deficiency diseases. Nicotinic acid is used solely as a vasodilator, on the assumption that it acts on central vessels as it does on peripheral, as a vasodilator. For this there is increasing evidence[8, 1] despite some evidence to the contrary.[7, 4]

Discussion

The evidence brought forward indicates, it is hoped satisfactorily, that the syndrome of Ménière and the syndrome of migraine are identical in as far as concerns the mechanism of their production, which is a vascular one. Where they differ is in the location of the impact—in the one case it is upon the labyrinth, in the other upon the cerebral hemisphere. What determines location or laterality is not as yet apparent.

The two syndromes differ, too, in the frequency of occurrence of the two groups. Whereas in Ménière's syndrome the primary vasodilator group is a relatively small one compared with the vasoconstrictor, in the migraine syndrome the position, if not reversed, is at least more nearly equal. Allergy as a cause of migraine is common, as a cause of paroxysmal vertigo it is uncommon. This fits in with the age groups in which the two syndromes arise—paroxysmal headache is a condition of youth, like the vasodilation which produces it, paroxysmal vertigo a condition of middle life or later, like the vasoconstriction which is its usual cause.

Finally, to repeat a point already insisted upon, nicotinic acid is used in the treatment of the vasoconstrictor group not because it is part of the vitamin B complex, but because it is a powerful capillary vasodilator. Nicotinic acid is used as the type substance to overcome vasoconstriction when the cause cannot be found, just as histamine is used as the type substance to test

for and desensitize against a general allergy when the specific antigen is not known. Neither method absolves us from a search for the specific cause if such can be found. But since in the present state of knowledge these specific causes are frequently unknown or undiscoverable, an understanding of the basic mechanism will when necessary permit of the effective use of a non-specific remedy. It is this basic vascular mechanism which presumably explains the satisfactory results reported with such divergent substances as thiamin chloride and estrogens—both have a certain vasodilator action apart from their specific replacement function.

Summary

1. The two groups into which cases of Ménière's syndrome can be divided have been shown to correspond etiologically to two groups of migraine cases.

2. Many instances arise in both groups of cases in which the two conditions are coincidental and apparently related, or in which migraine attacks merge into Ménière attacks.

3. The mechanism of both groups is discussed and an hypothesis put forward to explain the clinical phenomena observed.

4. Treatment which has proved successful in relieving the vertigo of patients with Ménière's syndrome has also relieved the migraine headache in those cases in which it also has been present.

5. Treatment of this syndrome, whether characterized in the main by vertigo or by headache, to be successful depends upon accurate grouping of cases. No single method will achieve success in all cases, for there is more than one cause.

Case Reports

Case 1. A Case of Severe Ménière Attacks (Vasodilator Type) Associated with Migraine Headaches. A woman aged 28 (1937) complained of attacks of vertigo of varying severity weekly for four months with slightly impaired hearing and tinnitus in the right ear. Since adolescence she had suffered from migraine, occasionally with blurring of vision. These migraine attacks had at one time occurred weekly, then had become less frequent, but since her dizzy spells they had become more frequent again and ushered in the attacks of vertigo. Examination of the ears showed slight impairment of hearing of conductive type on the right side and vestibular hypofunction on the right. Other examinations and investigations were negative. At that time she was put on sedation and a dietary régime and was not seen again for two years.

In February 1939 she returned with a story of improvement—headaches less frequent and less severe, a few mild dizzy spells—until two weeks previously when she had a severe attack of headache and vertigo followed by another the day before being seen. Hearing had somewhat deteriorated but was variable, as also was tinnitus. On examination the findings were the same as before except for a marked increase in hearing loss, and this time a histamine skin test was done which was markedly positive. Desensitization to histamine was undertaken, and for 12 months she had no dizziness or headache, though she still had occasional tinnitus and the hearing loss remained stationary. Then her headaches started to return and a feeling as

though a dizzy spell impended. She was given a short course of histamine injections, after the first of which symptoms disappeared and she has since been free of vertigo and almost of headache for 12 months (August, 1941).

Case 2. A Case in Which Ménière Attacks (Vasoconstrictor Type) Followed upon Cessation of Migraine. A woman aged 53 had suffered from severe predominantly right-sided migraine from age 10 to 25. This improved after marriage and her migraine eventually disappeared, though she had occasional headaches of indefinite nature. Then at age 33 she suddenly had a succession of mild dizzy spells ushered in by one severe one which occurred after a week of tinnitus and impairment of hearing in the right ear. Attacks continued to occur in batches, varying in severity, at intervals of two to three months, until she was seen (1940) following a series of rather unusually severe attacks. During the previous two years, headaches had returned, now without migraine characteristics, and had been getting more severe. The dizzy spells were typical Ménière attacks, and as usual findings were negative except as regards diminished function in the affected (right) ear. She fell into the histamine insensitive group and was consequently treated with nicotinic acid, since which time she has suffered no more dizzy spells (eight months). During this time she has had three mild headaches, not migraine in type—"the sort of headache I imagine everyone has once in a while, nothing like I used to have."

Case 3. A Case of Migraine Followed by Ménière Attacks in Which Eventually Headache Ceased but Scotoma Remained. A man aged 45 had suffered from left-sided migraine of considerable severity for 25 years, usually with visual disturbances. Seven years ago (1934) he had experienced his first dizzy spell, and attacks of vertigo had continued to occur during the next 13 months, accompanied by deafness and tinnitus. Then tinnitus and vertigo ceased, and deafness improved as far as he could tell to normal. Two years later (1937) he experienced four weeks of tinnitus without vertigo or apparently impairment of hearing. In 1939 he had three months of vertigo, deafness and tinnitus, and this time the deafness and tinnitus persisted though the vertigo ceased. In 1941 (March) he again had attacks lasting until seen. During these seven years his migraine headaches had gradually diminished in frequency and severity, and for the previous three months, the period of his most recent bout of Ménière attacks, they had virtually ceased (very occasional and very slight left frontal pain only), *but scotoma and fortification spectra had occurred without headache.* Examination demonstrated the usual absence of positive findings apart from the ear (diminished left cochlear function). The histamine skin test was negative, putting him in the vasoconstrictor group, and treatment on the appropriate lines was recommended. Unfortunately it has not been possible to follow up this patient.

The great interest of the case is in the onset or persistence of vasoconstrictor mechanisms—vertigo and scotoma, with the gradual failing and ultimate disappearance of the secondary vasodilator phenomenon of headache.

Case 4. A Case Showing a Scotoma without Headache but with Other Migraine Manifestations. A woman aged 39 years in 1938, two and a half years before being seen, had noticed a left paracentral scotoma which appeared *suddenly* at the end of a busy day spent largely under arc lights. This confused the issue at first, making a Kleig burn seem probable, but subsequent events invalidated this diagnosis. The scotoma slowly increased in size and intensity for three months, then as gradually faded away. At no time was there complete loss of vision, but sight was blurred and objects appeared as through a fog. Spots and flashes of light were common, but she never experienced fortification spectra, and the degree of impairment was very variable. Sometimes the fog would be thin and the scotoma small, at others thick and the scotoma large. These changes could happen very suddenly. The whole episode lasted about six months. A second similar episode occurred a year later, again after considerable stress, and she was in the third when first seen.

There were certain other significant points in the history. She had never suffered from headaches, but there was a family history of migraine, asthma, hay fever and eczema. She herself had suffered from "bilious attacks" since the age of 15 and had to be careful of her diet. For some years she had been subject to bouts of sneezing, especially on rising in the morning. Two months before the scotoma appeared for the first time, also after a long and busy day, she had a sudden attack of weakness, collapse and "black-out" with a pulse that dropped to 50 for 15 minutes, or more. This sudden bradycardia had returned on many subsequent occasions, though only for two or three minutes at a time and always during periods when the scotoma was present, though it was not synchronous with the onset of the scotoma. Alcohol, in the form of a cocktail, undoubtedly was capable of diminishing the size of the scotoma and the density of the fog, an observation made on several occasions. An injection of ergotamine on one occasion produced no improvement; if anything it made matters worse.

Examination revealed nothing of significance, apart from the ophthalmological findings, and a somewhat excessive weight. Nor was there anything of significance in the eye examination apart from the variable left paracentral scotoma. Laboratory investigations contributed no information of help: basal metabolic rate was —2, sedimentation rate 7, sugar tolerance normal. A histamine skin test was negative.

It was assumed that the mechanism at work was a vascular one comparable to that producing migraine and Ménière attacks, that the scotoma represented a condition comparable to the pre-headache phase of migraine, and that it was vasoconstrictor in type in view of the normal histamine reaction. This assumption received added support when an injection of acetylcholin 0.1 gm. produced an improvement in the size and depth of the scotoma. She was consequently treated on vasodilator lines with nicotinic acid, at the same time being given a mildly reducing diet of high protein, high vitamin content and a small dose (gr. ½) of thyroid extract daily. She was also urged to reorganize her life, to live at a slower pace and under less extreme conditions. This of course she did not do. Nevertheless she started to improve immediately after treatment was instituted (it may be that it chanced to be instituted at a lucky moment) and continued to improve rapidly, more rapidly according to her own testimony than she had ever done before. In two months the scotoma had almost disappeared, vision had improved, she had lost 15 lbs. in weight and was feeling in much better general health. In six months there has been no set back, even though she has been grossly overworked and has had two attacks of a vasovagal nature in that time. A very small scotoma remains which has not varied in four months and which one fears may represent permanent damage. It does not bother her. What is equally worthy of note is that since she has followed this régime, she finds that she can tolerate foods which formerly she could not (tomatoes, chocolate, fats) and her sneezing has ceased. Though it is too early to be certain of success in view of relapses in the past, the improvement in collateral symptoms under treatment suggests that it is properly directed and that the assumed mechanism may be correct.

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ARACHNOIDITIS (DIFFUSE PROLIFERATIVE LEPTOMENINGITIS) *

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Chronic or subacute low-grade leptomeningitis, cystic and adhesive in nature, is a clinicopathologic condition known by a number of names in medical literature (arachnoiditis, serous meningitis, meningitis serosa circumscripta vel cystica, arachnoiditis adhesiva circumscripta and diffusa). For the sake of simplicity and because of widely accepted usage in this country, the term arachnoiditis is used in this title although it is obviously inaccurate.

The cystic structures are not cysts in the true sense of the word. They are in reality collections of cerebrospinal fluid walled off by meningeal adhesions. The fluid within the cysts is often under great tension. The leptomeningitis may be predominantly cystic or predominantly adhesive. The extent of the arachnoiditis varies from a well-localized lesion to a diffuse process involving the entire cerebrospinal axis. There is, however, a definite tendency for the process to be either cerebral or spinal. Arachnoiditis may be primary or it may be secondary to pathologic changes in adjacent structures.†

In some instances the etiology can be ascertained. This is especially true in the localized (circumscribed) form in which trauma has been shown to play an important part. The clinical picture, the course, and the response to treatment are extremely variable, depending upon the location, the extent and the cause of the process.

The cerebral type of arachnoiditis is usually focal in type but rarely it may be diffuse. Demel [1] collected reports of 40 cases of the localized type. The clinical picture was that of brain tumor. In 16 cases the lesion was in the posterior fossa. Recovery followed in approximately 90 per cent of cases operated upon. Horrax [2] reported 33 cases simulating cerebellar tumor; 28 were followed from one to nine years, and all showed improvement or complete relief from symptoms. Lillie [3] reported three cases of prechiasmal syndrome produced by arachnoiditis. He indicated the possibility of preoperative diagnosis and the favorable results from proper surgical treatment.

For purposes of discussion, spinal arachnoiditis may be divided into the localized and the disseminated types. Generally, writers on the subject of

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† In the various types of encephalitis and in other diseases of the nervous system, leptomeningeal thickening is a not infrequent pathologic finding. In these instances, however, the leptomeningeal thickenings do not necessarily produce symptoms. Here we are concerned only with the type of arachnoiditis which causes symptoms.

spinal arachnoiditis group all the cases together regardless of the extent of the process. This gives an exceedingly varied and complex clinical picture. The tendency to put all cases into a single group is due in part to the clinical difficulty of differentiating the two types. However, as Stookey [4] points out, the subject would be less confusing if a real effort were made to place the disseminated and localized types in separate categories for the purpose of analysis. In the following discussion an effort will be made to distinguish between the circumscribed and the disseminated types. If that is not possible, the term arachnoiditis will not be qualified.

Elkington [5] reported 41 cases of arachnoiditis collected at National Hospital, Queens Square. There were 30 males and 11 females. The youngest case was 23 years of age; the oldest 65. The average age of the patients when first seen was 45 years. The age grouping was as follows:

Under 20— 0 cases
20–30— 6 cases
30–40— 6 cases
40–50—14 cases
50–60—10 cases
60–70— 5 cases

One of the cases reported by us is that of a 17-month-old boy. Elkington refers to the case of an 8-year-old boy reported by Heller. In Elsberg's [6] 38 cases, men and women were equally affected.

As to causes, Elkington's 41 cases are divided in the following manner:

9 cases—Injury. The interval between injury and symptoms varied from three weeks to 24 years. The severity of the injury was inconstant.
4 cases—Syphilis.
2 cases—Meningococcic meningitis.
4 cases—Gonorrhea.
16 cases—"Systemic" infection.
18 cases—No known cause.

Ten of 12 cases of spinal arachnoiditis reported by Stookey had had typhoid fever, influenza, encephalitis, or meningitis. Trauma as a forerunner of arachnoiditis (localized?) is reported particularly by Mauss and Krüger.[7] In 54 laminectomies in cases of individuals who suffered war wounds, they found arachnoiditis 23 times. In 14 of the 23 cases there was direct trauma of vertebrae. In nine cases there was no direct vertebral trauma. The authors attributed these cases to concussion associated with momentary dislocations of the vertebral bodies. They reported good results from operative intervention. As to causes of the disseminated type, Selinsky [8] reported that five of eight cases had had pneumonic or pleuritic infections. Mackay [9] reported five cases of the disseminated type; three seemed to result from some form of acute meningitis—one five weeks, one

17 years, and one five years previous to the arachnoiditis. In two cases there was no known cause. Barker and Ford [10] reported a case of the disseminated type in which arachnoiditis set in during convalescence from lymphocytic choriomeningitis. Laboratory studies revealed the virus.

Clinical Picture. There is a gradual onset without fever. Invariably the disease assumes a subacute or chronic course. In Stookey's 12 cases of arachnoiditis, six had symptoms for more than seven years. In Elsberg's series there was a history of symptoms for from one to more than nine years. The disseminated type produces a syndrome of multiple involvement of the spinal nerve rootlets, both anterior and posterior, but predominantly posterior. *Pain is the most distinctive symptom.* It usually commences over one or more spinal segments and later becomes bilateral and spreads over a wide cutaneous area. The pain often has a burning, constricting quality and is frequently influenced by posture, movement of the spine, straining and coughing. The pain may occur over widely separated areas and may be accompanied by hyperesthesia or diminished sensation. The objective sensory disturbances are often vague, bizarre, or inconstant in distribution. Diminished reflexes and muscular atrophy which can best be explained on the basis of anterior rootlet involvement are not infrequent. If the cauda equina is involved there is atrophy and hypotonia of the legs. Bladder and rectal disturbances come late in the disease; as a rule there is urgency long before incontinence sets in.

There may be slight or, in later cases, considerable involvement of the spinal cord. A cyst may produce signs and symptoms of compression like a true neoplasm. If the cyst is part of a disseminated process, there will be signs simulating extramedullary tumor in addition to the features of multiple rootlet involvement. This will lead to slowly progressive weakness and spasticity of the extremities, impaired sensibility, exaggeration of tendon reflexes, pathologic plantar responses, and impairment of sphincters. Constriction of the spinal cord by adhesions may cause a similar picture.

In 50 per cent of Elsberg's cases, cells and total protein were well within normal limits. Stookey made manometric studies in 10 cases; five had almost complete block and five showed partial block. Even in some cases of subarachnoid block, the protein content of the fluid was normal and xanthochromia was absent. Increase in cells is rare in arachnoiditis. In Elkington's series, cytologic studies were made in 26 cases with normal results in 25. In one case there were 50 and 42 lymphocytes per cu. mm. on two separate occasions.

In Selinsky's eight cases of disseminated arachnoiditis all showed scattered arrest of iodized oil after cisternal injection. The arrest of lipiodol at multiple levels is pointed out by a number of writers. Schwartz and Deery [11] describe small linear shadows due to droplets of oil spread over portions of the meninges. Scattered droplets of oil in the subarachnoid space generally retain a globular shape. However, when the oil lodges

against thickened dentate ligaments and subarachnoid fibers, small linear horizontally placed shadows are produced on the film.

Robertson [12] reported five cases of arachnoiditis. He made the preoperative diagnosis in three of the cases, using the following points:

1. Extensive area affected by the pain which was of burning quality and characterized by periods of remission.
2. The intimate relation of pain to posture (such as raising the arm).
3. Evidence of dissemination of the process.
4. Evidence of involvement of motor roots (atrophy and diminished reflexes).

The pain is intense and is frequently associated with hyperesthesia. In two of our cases the pain was intractable and disabling. The duration of the symptoms is usually much longer in arachnoiditis than in cord tumor. The initial pain frequently extends over a larger area than in cord tumor (for example, an entire extremity). The distribution of the pain is difficult to reconcile with a single compressing lesion. Anesthesia is generally not so pronounced as in spinal tumor, unless there is marked constriction. A history of previous subarachnoid infection is helpful in the diagnosis of arachnoiditis. The arrest of iodized oil at multiple levels is a most important diagnostic aid. Subarachnoid block without xanthochromia or increased protein is a highly suggestive corroborative finding in arachnoiditis. The onset of arachnoiditis is much slower than in encephalo-myelo-radiculitis.[13] In the latter there is rarely subarachnoid block and the course is very much more benign. In encephalo-myelo-radiculitis there is, as a rule, absence of muscle atrophy and fairly complete recovery despite the severity and extensiveness of the nervous system involvement. In arachnoiditis there is rarely cell protein dissociation. Evidence of upper and lower motor neuron involvement in arachnoiditis may lead to a mistaken diagnosis of amyotrophic lateral sclerosis. This occurred in one of our cases and in a case reported by Robertson. However, pain is rarely a prominent feature of amyotrophic lateral sclerosis and subarachnoid block practically never occurs.

Treatment. Elsberg states: "Whatever may be the cause for the leptomeningeal adhesions, it can not be denied that the adhesions may disturb the functions of the spinal cord and nerve roots by direct pressure, and by interference with the vascular supply of the cord aggravate a preëxisting intramedullary lesion. Therefore, in the present state of knowledge, exploratory laminectomy is generally indicated." . . . "The adhesions are most often found on the posterior and lateral aspects of the spinal cord and especial attention must be paid to the emerging nerve roots, and any bands constricting them must be divided."

In referring to roentgen-ray therapy for disseminated arachnoiditis, Selinsky states: "In my experience, no other nonsurgical therapeutic measure has exerted such a favorable influence. The spine is crossfired with high voltage radiation at the various levels indicated by the sensory disturbance.

One or more series of treatments are given, depending on the response to therapy. If indicated, the series of treatments is repeated at intervals of six weeks. Fractional treatments are given at each sitting and consist of from 100 to 150 roentgens (in air) until a total of 800 roentgens is administered." According to Selinsky: "High voltage roentgen therapy exerts a definitely ameliorating effect which is variable in duration. Recurrences of the pain may be relieved by a repetition of the treatment." He reported "good results" in four of eight cases. Operation was done in Mackay's five cases of the disseminated type; two died, two were unimproved, and one was clinically benefited.

From a pathologic study of our cases of disseminated arachnoiditis, the outlook for therapeutic improvement from either roentgen-ray or surgical intervention after the process has been long established, does not appear at all promising. In our four cases the cord damage appeared to be due to vascular involvement with associated tissue destruction rather than compression of the nervous tissue by the thickened meninges.

Elsberg states: "The outlook after operation will depend to a considerable extent upon the intramedullary changes that have occurred. If the adhesive process is well localized and the symptoms have not been of more than one or two years' duration, the patient may be relieved of all or almost all disturbances by the operation." . . . "If the adhesive process extends over a great part of the spinal leptomeninges, the outlook for improvement is small. However, some of these patients may be improved if by good fortune or good judgment, a part of the cord which has been most compromised by the adhesive process has been exposed and adhesions which compressed the cord have been divided or the contents of a cyst evacuated." Elsberg analyzed 38 cases from his personal experience. "In more than one-half the patients, little or no improvement followed the surgical intervention." . . . "In about 25 per cent of the patients in whom the adhesive process appeared localized with or without compression of the cord by bands, and in whom the symptoms were of less than two years' duration there was considerable improvement in the spastic paraplegia and the sensory disturbances, so that bedridden individuals were able to be up and about again; bladder disturbances, when they existed, were not relieved, and the patient remained an invalid."

In about 25 per cent of Elsberg's patients the relief was complete or almost complete, so that the individuals were able to return to their work and usefulness. In the majority of these patients the relief was permanent.

Pathologic Findings. In chronic diffuse leptomeningitis there is grossly a definite thickening of the leptomeninges throughout the entire length of the spinal cord. Usually this involvement is not uniform, being more marked at certain levels and in certain regions at a single level. In the more involved areas the membranes are opaque and completely obliterate the underlying structures.

In Elkington's series, 18 of 41 cases showed at operation a loculated collection of fluid amounting to actual cysts. The most conspicuous abnor-

mality was in the arachnoid which was often milky and opaque in appearance and contained areas of irregular patchy thickenings. The pia-arachnoid was bound to the dura, the cord, and the nerve roots by adhesions. In some of the cases there was a complete obliteration of the subarachnoid space.

Since there are very few complete autopsy studies reported in this condition, we shall limit the histopathological descriptions to the study of our own cases. Before describing the pathologic changes in chronic diffuse leptomeningitis, it might be advisable to review briefly the structure of the

FIG. 1. Thickening of the leptomeninges. These membranes are four times normal thickness and are composed of relatively acellular collagenous tissue. Hematoxylin-eosin stain.

normal spinal pia-arachnoid. The spinal pia is composed of a relatively thin layer of intertwining collagenous fibers which are closely adherent to the surface of the cord. The thickness of this layer varies normally from five to 15 microns. The pia is very vascular and contains a large number of blood vessels. Along those vessels one can normally observe scattered groups of mononuclear cells which often increase in number in inflammatory conditions. The arachnoid is a thin net-like membrane about three times as thick as the pia, measuring about 30 to 40 microns. It is a relatively avascular membrane composed of collagenous fibers and lined on both its inner

and outer surfaces by a thin cellular endothelial layer composed of a single irregular layer of peculiar squamous cells which can usually be identified only by means of special silver stains. There is a definite space between the pia and arachnoid called the subarachnoid space. The latter is traversed by numerous fibrous strands that extend from the arachnoid and are attached to the pia (arachnoid trabeculae). When the leptomeninges are studied in fixed tissue, many of these details cannot be made out. Often the subarachnoid space is greatly narrowed and the leptomeninges are so intimately

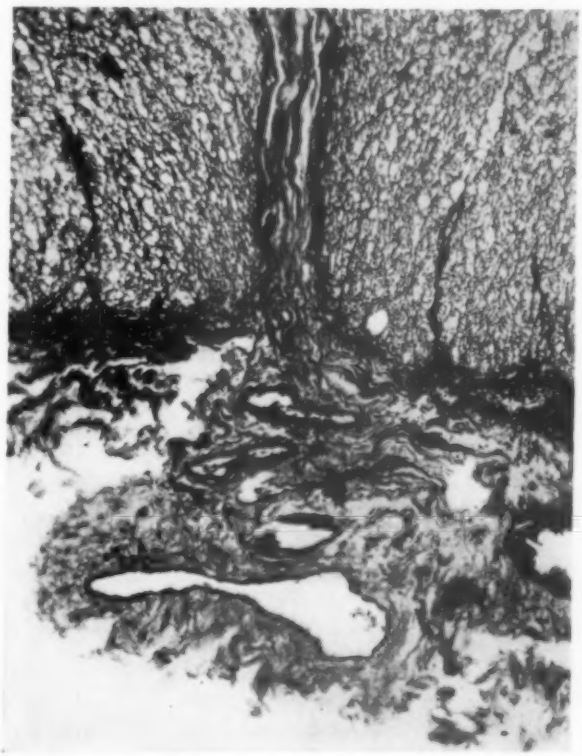

FIG. 2. Compression of the radial vessels by the thickened pia-arachnoid. There is no complete occlusion of the vessels although their lumina are markedly narrowed. Phosphotungstic acid-hematoxylin stain.

related that they appear as a single structure. They then appear as interlacing bundles of collagenous fibers, the inner portion being vascular and probably representing the pia whereas the outer portion is relatively avascular, somewhat thicker, and represents the arachnoid. The total thickness of the leptomeninges normally would vary from 35 to 55 microns.

Histologically, in arachnoiditis there is a diffuse but irregular thickening of the leptomeninges, their combined thickness often varying from 85 to 215 microns, i.e., two to five times normal (figure 1). Either of the two membranes may be more severely involved, but often they are so intimately

related that it becomes impossible positively to identify the separate membranes. In most areas there is a complete obliteration of the subarachnoid space, although occasionally in the less severely involved areas this space can still be identified although greatly reduced in size. In some cases the thickening of the leptomeninges may become so extensive that the process extends outward to obliterate even the subdural space, the thickened membranes merging with the inner dural layer which, however, can usually be identified by its more dense structure. This thickening of the leptomeninges may or

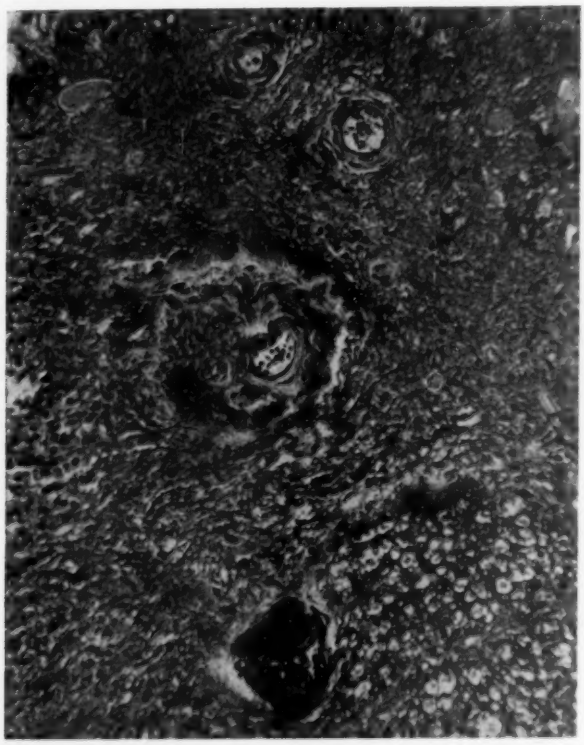

FIG. 3. Involvement of one of the smaller paracentral arteries by the thickened leptomeninges. Phosphotungstic acid-hematoxylin stain.

may not extend inward to involve the membranes within the anterior and posterior commissures of the cord.

The involved pia-arachnoid shows definite structural variations. It is usually definitely acellular and comprised of dense collagenous tissue. Often it becomes partially or even completely hyalinized, losing all structural characteristics and assuming a homogenous appearance. A few connective tissue nuclei can be found in such cases but even these are pyknotic. Scattered collections of mononuclear cells are occasionally present (figure 1).

The spinal vessels show a most variable degree of involvement. The radial vessels surrounding the cord are invariably compressed by the thick-

ened membranes and many are completely occluded (figure 2). The degree of vascular involvement frequently is in direct proportion to the thickness of the pia-arachnoid. The vascular pia, in some cases, appears entirely devoid of vessels whereas in other cases it shows a definite reduction in its vascularity. The sulcal arteries are usually completely surrounded and often compressed by the thickened membranes resulting, in many cases, in a definite vascular narrowing. In a few areas these vessels are completely occluded and produce a focal softening or even a complete central cavitation within

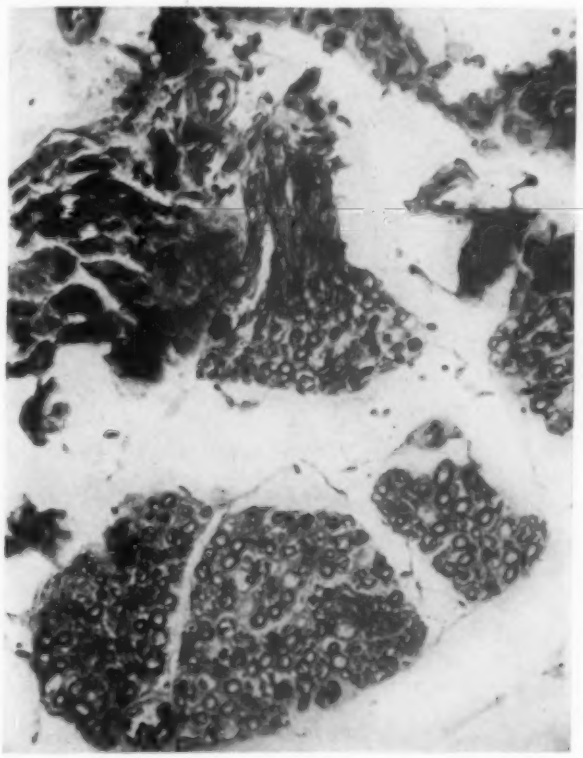

FIG. 4. Narrowing and compression of one of the rootlets as it penetrates the thickened leptomeninges. Note the demyelinization of the rootlet and its partial replacement by connective tissue. Phosphotungstic acid-hematoxylin stain.

the spinal cord. Usually the smaller paracentral arteries escape damage, but in an occasional area even those vessels become compressed and occluded (figure 3).

The spinal rootlets as they penetrate these thickened membranes may remain uninvolved, but more commonly they are narrowed, compressed and show definite pathologic alterations. Demyelinization is invariably present with a variable degree of destruction of nerve fibers and a secondary fibrous tissue replacement of the involved structures. In some rootlets almost half the fibers appear to have been replaced by a secondary fibrosis (figure 4).

The spinal cord usually shows changes at some levels. These alterations appear to be directly related to the degree of vascular involvement. The meningeal thickening does not appear sufficient to produce cord compression. The cord shows a moderate swelling of the myelin sheaths, often with some patchy vacuolization. In some cases, vascular occlusion produces definite focal areas of softening which involve large areas of a single cord level. Even complete central cavitation may occur, producing a typical syringomyelic picture. The nerve cells are usually uninvolved, although moderate changes may occur in the more severe cases, consisting of swelling, chromatolysis, fragmentation and even complete disappearance. In some cases petechiae occur throughout the gray matter of the cord.

Case Reports

Case 1. On September 1, 1937, H. S., a 57 year old white male, while fixing a tire, stumbled backwards and struck the lower part of his back against a cement curb. He got up without assistance and continued his work. During the following days the base of his spine felt sore, usually becoming worse at night. However, he continued to work regularly. On September 14, two weeks after his injury, he noticed muscular twitching in the right thigh. The next day he had pain and numbness in the lower back and about the right hip. On the same day, while trying to rise from a stooped position, he lost control of both legs. This was followed almost immediately by severe pain extending down to both feet. In three or four hours his legs became completely paralyzed and remained so for about five weeks. He had bowel and bladder incontinence for the first three weeks of that period. He had a patchy sensory loss from the umbilicus down. After three weeks, his urinary difficulty disappeared. However, he did not regain rectal sensation. After five weeks, control of the legs began to return. At the same time he noted gradually increasing stiffness of the legs. A "burning feeling" was associated with the stiffness and return of motion. He was able to walk with some support. He continued to have pain in the lower back and legs.

About 15 years prior to the difficulty already described he had suffered a slight head injury. Six weeks later he had dizziness and pains in the neck. The dizziness was brought on by rotation of the head, and he had some difficulty maintaining his balance. He had no paralysis, and the symptoms disappeared in three weeks.

He was admitted to the University Hospitals on December 23, 1937, at which time the neurologic examination revealed: hearing loss on the right; hyperactive deep reflexes in the legs with bilaterally positive Babinski signs; positive Chaddock and Oppenheim signs on the right; left patellar and bilateral ankle clonus; weakness and spasticity of the legs; incoördination of the legs with loss of position sense and diminished vibratory sensibility; absence of pain, temperature and light touch sensibility from the twelfth thoracic segment down. The rest of the physical examination was essentially negative.

The spinal fluid examination revealed a pressure of 10 mm. of mercury with no rise on jugular compression; protein, 56 mg. per cent; no cells, and serologic tests negative for syphilis. Urinalysis and routine blood studies were normal.

Roentgen-ray report: "Lipiodol examination of the spine was done radiographically and fluoroscopically after the injection of 2.25 c.c. of lipiodol into the cisterna magna. At the beginning of the examination all of the lipiodol was in the upper cervical spine and cisterna. After putting the patient in the upright position the lipiodol moved very slowly through the cervical canal and met a temporary obstruc-

tion at approximately the level of the first thoracic vertebra. After approximately four to five hours in the upright position there was still lipiodol retained at the level of the sixth thoracic, eleventh thoracic and second lumbar vertebrae. A few droplets had dropped down into the sacral canal. In one of the lateral views at the level between the first and second lumbar vertebrae there was a suggestion of posterior bulging into the canal from the intervertebral disc. Findings suggest an arachnoiditis

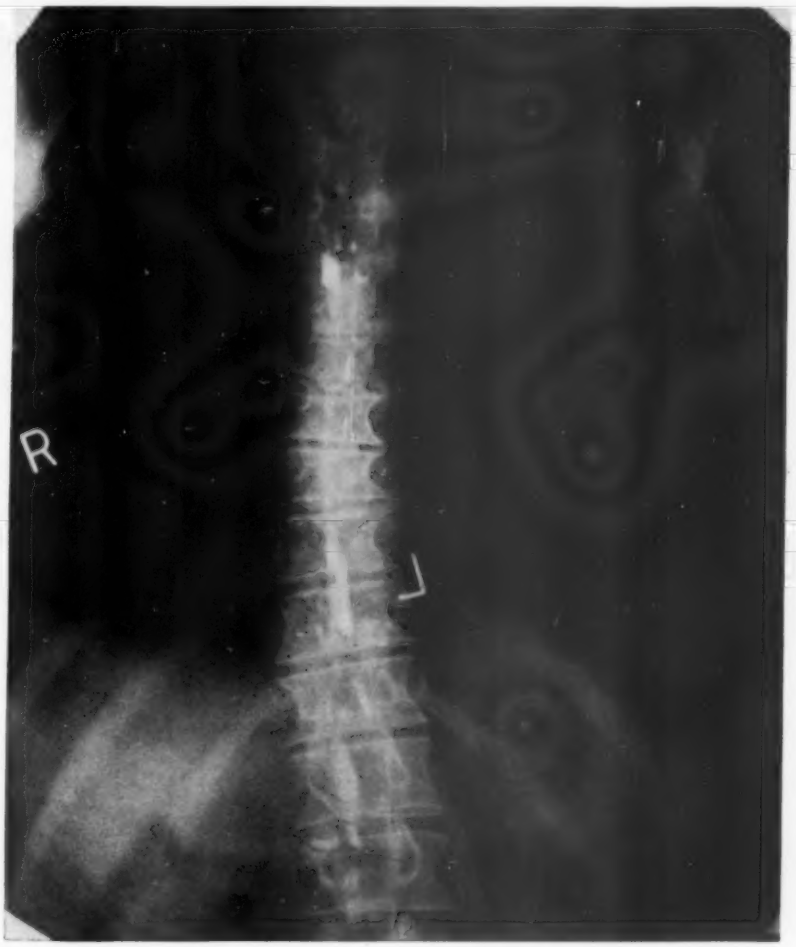

FIG. 5. Arrest of lipiodol at multiple levels in a case of arachnoiditis.

together with the possibility of multiple ruptures of the intervertebral discs. A definite diagnosis can not be made" (figure 5).

On January 11, 1938, the lamina of the first and second lumbar and the twelfth thoracic vertebrae were removed, and there was apparently some encroachment on the cord at this level. There was no pulsation of the cord. The conus region was exposed. The rootlets seemed to be very thick and heavy as though they were swollen. A slightly protruding intervertebral disc was found. It did not appear to be ruptured or prolapsed in the usual manner. It was simply compressed back into the spinal canal

for an elevation of about 3 or 3½ mm. Through an incision in the anterior surface of the dura part of the disc was excised and part of it was curetted out. A small amount of lipiodol seemed to be held in position just above the protrusion. The rest of the lipiodol could not be evacuated by changing the patient's position.

The postoperative course was very stormy. On January 18, 1938, the blood culture was positive for hemolytic streptococci. The patient developed uncontrollable abdominal distention. Despite treatment by sulfanilamide, nasal suction and other measures, he failed to rally and died on January 20, 1938, about five months after the onset of his illness.

Pathological studies: The leptomeninges surrounding the entire cord were thickened, both membranes being about equally involved and measuring from 55 to 210 microns in thickness. The subarachnoid space was narrowed and in some areas completely obliterated. The pia-arachnoid appeared avascular, acellular and somewhat hyalinized. Not even the remnants of pyknotic nuclei could be detected. The arachnoid trabeculae were narrowed and thickened. The membranes within the commissures were also greatly involved. The sulcal arteries were completely surrounded and compressed by the thickened meninges, producing a definite vascular narrowing. Even the smaller paracentral arteries were partially compressed by the extensive meningeal changes.

The rootlets as they passed through the thickened meninges were greatly constricted and appeared to have undergone partial destruction. They showed a great decrease in the number of myelin sheaths with a secondary fibrous tissue replacement of the destroyed elements. Almost half the rootlet fibers appeared to have been replaced.

The spinal cord showed a moderate demyelinization which was particularly marked in the posterior columns. The nerve cells appeared structurally intact.

Case 2. J. J. was 51 years of age at time of death, November 1940. In May of 1937, the patient first noted an itching sensation in band form at the level of the nipple line. At the time of examination, a burning and smarting sensation replaced the itching. The sensations were intermittent, coming in the form of attacks as frequently as every five or six seconds on one side or the other. Two days after the onset of the difficulty his appendix was removed at another hospital. A week after operation the right leg became numb and he experienced some difficulty in walking. In a few weeks the left lower extremity became numb. He stated that when he crossed his legs in bed he was unable to determine which leg was on top. He first entered the Hospital three months after the onset of his illness. His chief complaint was numbness and loss of sensation in the legs from the hips down to and including his feet. He also complained of a constricting sensation around his waist.

His past history and family history were essentially negative. In March 1937, the patient wrenched his back while lifting a heavy box. He was not able to work for two weeks.

Physical examination was negative except for the following neurologic findings: The cranial nerves were essentially normal except for diminution in visual acuity on the right. He was unable to read large newsprint with the right eye. The upper extremities were normal, except that the right triceps reflex was more active than the left. Only the right upper abdominal reflex was elicited. There was spasticity of the legs, with hyperactive deep reflexes and positive Babinski sign bilaterally. There was marked weakness of the right leg. Vibratory sensibility, muscle pain and position sense were normal in the left leg but markedly impaired in the right leg. Light touch and pin prick were felt normally down to the third rib on the right and the fourth rib on the left; below these levels there was patchy loss of superficial sensation. There was no sphincter impairment.

Laboratory studies, including tests for syphilis, on the blood and spinal fluid, were negative. There was no evidence of subarachnoid block. The spinal fluid was clear and colorless, contained 40 mg. of protein per cu. mm., and no cells. The gold curve was 022110000.

Roentgenographic studies of the spine with the use of lipiodol were negative.

About three weeks after his hospital admission, the patient experienced some improvement. His legs improved in strength and his sensory disturbances were not so severe as previously. He was discharged in September after one month of hospitalization. However, his improvement was of brief duration, and he was readmitted in October 1937. In November 1937, a laminectomy was performed in the region of the seventh cervical and first thoracic vertebrae. There was no obstruction. The cord appeared normal. The arachnoid seemed thickened in several places. His postoperative course was uneventful and he was discharged unimproved. He was followed in the outpatient department from that time until his final hospital admission in 1940. He complained bitterly of constant itching and burning sensations. He was unable to sleep, lost weight, and gradually became weaker. He seemed to improve following a course of deep roentgen-ray, but his improvement was again of short duration. His weakness became so marked that it was necessary again to admit him to the hospital in September 1940. At that time he complained of bladder and rectal incontinence of three or four months' duration. During the last six months previous to admission it was difficult for him to walk because of weakness of the legs. He had last reported two weeks prior to admission. He first had numbness of both hands and then his left hand became paralyzed. Neurologic examination showed spastic paralysis of both legs and atrophy of the small muscles of the hands. The left hand was flexed at the wrist and the fingers were flexed in the form of a cup. Both arms showed a patchy superficial sensory loss. The patient developed signs of urinary tract infection. He became weaker, developed a pneumonic process in the right lung, and died on November 6, 1940, about three and one-half years after the onset of his illness.

Pathologic finding: Autopsy revealed a pneumonic process in the right lung. Serial sections of the brain revealed no gross abnormalities. The dura was normal except for thickening in the operative region. The arachnoid showed yellowish, thickened, indurated areas averaging about 5 mm. in diameter and scattered throughout the thoracic and lumbar areas. There was atrophy of the upper thoracic and cervical regions of the spinal cord with small areas of hemorrhagic softening.

Microscopic studies showed a moderate diffuse thickening of the pia-arachnoid throughout all levels of the cord. This alteration was most marked in the pia, which measured 15 micra in thickness, was very acellular and contained very few vessels. The arachnoid was less severely involved but was also definitely thickened, especially in the anterior and posterior aspects of the cord. The extensions of these membranes into the commissures showed a similar structural alteration and thickening. The rootlets were completely surrounded by these thickened meninges but showed no structural alterations.

The sulcal arteries were for the most part uninvolved. In a few areas their lumina were narrowed. In some of the sacral segments these vessels appeared completely occluded and had produced a focal softening within the cord. Sections through the upper sacral and lower lumbar levels revealed a complete central cavitation of the cord. The tissues around this cavitation were fragmented but showed a minimal degree of cellular reaction.

The spinal cord showed a diffuse swelling of the myelin sheaths and some swelling of the anterior horn cells. Numerous distended vessels and petechiae were present throughout the gray matter of the cord.

Case 3. A. M., a white male, was 57 years of age at time of his death in August 1940.

The patient was admitted to the General Hospital in January 1940, complaining of pain and weakness of the left leg, numbness and a sensation of cold in the toes and inability to walk. The symptoms began seven months previously with pain in the left ankle. In a few weeks the pain began to spread, gradually involving the calf, knee, thigh, and hip on the left side. The pain was steady, aching in character, and made worse by cold. It was noticed that his toes would readily become damp and cold. This was more marked in the left foot. Several months after the onset of the illness, the patient developed marked weakness in the left foot. For a few months prior to admission he had had urinary frequency.

Physical examination revealed a well-developed, obese white man who did not appear to be acutely ill. His feet were cyanotic and cold to the touch. The upper extremities were essentially normal. There were fibrillary tremors in both thighs and a flaccid paralysis of the left leg with absent deep reflexes and foot drop. The right leg was very weak. There were patchy scattered areas of hyperesthesia.

Laboratory studies showed a hemoglobin of 91 per cent and a white blood count of 6,050. The spinal fluid was clear and contained 50 mg. per cent of protein and no cells. The pressure and response to the Queckenstedt test were normal. Air myelography was negative.

Course: The patient complained constantly of pains in his legs. In May 1940, about one year after the onset of his illness, there was definite atrophy of both legs from the hips down. At that time he complained of paresthesias in both hands. In June he contracted lobar pneumonia which developed into a chronic unresolved process. In August a neurologist recorded atrophy of the muscles of the arms with marked weakness and flaccid paralysis of both legs with marked atrophy. The patient gradually became weaker, developed pneumonia on the right side, and died in August 1940, about 15 months after the onset of his illness.

Pathologic findings: The spinal cord and meninges were grossly normal. The vessels at the base of the brain revealed a moderate degree of arteriosclerosis. Serial sections of the brain showed no gross abnormalities.

Microscopic sections revealed a diffuse but irregular thickening of the spinal leptomeninges, which measured from 80 to 175 micra and produced a partial obliteration of the subarachnoid space. These membranes were extremely fibrous and relatively acellular, although they did contain a few nests of mononuclear cells. The vessels surrounding the cord were markedly compressed by the thickened meninges within which they were enmeshed. Some of the vessels were almost completely occluded.

The rootlets as they passed through the involved membranes did not appear to be extensively altered although in some of the lumbar segments there did appear to be a mild compression of the posterior rootlets with some replacement of the destroyed elements by connective tissue.

The cord appeared intact, neither the white nor gray substance showing any changes.

Case 4. (This case is being reported through the courtesy of Dr. A. H. Wells, Duluth.) G. H. was a male child who was 17 months of age at the time of his death in May of 1940. The patient was dead on admittance to the hospital, and there is, therefore, scant clinical information. He had been in a hospital about two months before his death. At that time it was noted on admission that the child had been sick for two weeks with fever and loss of weight. He had developed cough and dyspnea and had refused food for the last two days before admission.

The physical examination revealed râles in both lungs and extreme malnutrition. The reflexes were normal.

A physician who had attended him reported that the child developed normally until 11 months of age, when he first showed symptoms. In a short time he was unable to sit up and could not eat well. Two months before death he developed a severe bronchopneumonia. Following that illness he became very much weaker; he lay in bed, hardly moving a muscle.

Pathologic findings: The autopsy, performed three hours after death, revealed a bronchopneumonia and acute pancreatitis. Postmortem tests showed a blood sugar of 30 mg. per cent, and a urea nitrogen of 47.3 mg. per cent.

Microscopic sections revealed a fibrosis of the pia-arachnoid throughout the entire spinal cord. These membranes were greatly thickened, and this had resulted in a complete obliteration of the subarachnoid space. In many areas the collagenous pia-arachnoid fused imperceptibly with the dura, thus also obliterating the subdural space. The arteries surrounding the cord were compressed but not completely occluded by the meningeal involvement. The nerve rootlets were encircled but not particularly altered. The only changes seen in them were scattered areas of myelin swelling with an early formation of geometric figures due to the breakdown of the neurokeratin network.

There was a decrease in the number of nerve cells in the anterior horn, the remaining neurons being pale, fragmented or shrunken. Many ghost cells were observed. Numerous petechiae were present within the gray matter and especially near the dorsomedial cell columns. A small cystic area was encountered in the gray commissure lateral to the central canal. The white matter of the cord appeared to be intact. There was a little swelling of the myelin. This was most pronounced in the marginal region of the lateral columns.

Summary

The clinical course and the autopsy findings in four cases of disseminated arachnoiditis are recorded. One case is that of a 17-month-old boy.

The roentgenographic findings following cisternal injection of lipiodol are characterized by arrest of the oil at multiple levels.

Rootlet pain over widely separated areas and evidence of anterior rootlet involvement are suggestive diagnostic features.

The rootlet involvement is due to impingement by the proliferative leptomeningitis.

The intramedullary cord changes are frequently due to vascular narrowing and occlusion, because of the proliferative perivascular reaction.

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NEW TRENDS IN THE TREATMENT OF CHRONIC DISEASE: AN EXPERIENCE IN SPA THERAPY*

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FROM the dawn of civilization man has sought relief for his physical ailments. These, at first, were mainly acute in nature owing to the dangerous life which he lived in conflict with man and beast. Chronic disease early affected civilized man as has been proved by finding changes suggestive of arthritis and vascular disease in Egyptian mummies.

As a corollary to seeking relief, man has sought for the elixir of youth, that spark which would allow him to continue with unabated vigor the activities of youth even though age be at hand. In ancient Greece, many sought the waters with this object in view. In more recent times, glandular transplants were attempted, and during the past decade many glandular extracts and other products have been studied with the hope that some preparation might alter or stop the progressive changes which are associated with aging or the development of chronic disease.

Striking advances have been made in these studies, including the development of insulin, liver extract, sex hormones and vitamins—all valuable in the relief of disabling conditions. Yet the problems of increasing chronic cardiovascular disorders and the time-robbing disabilities of rheumatic ailments still challenge our thought and study. Improved methods for preventing and treating infections which formerly took a large toll in the younger age groups have saved the lives of many thousands of people who now have reached the middle and later decades where the degenerative chronic conditions are the principal causes of disability and death.

A. Are Cardiovascular and Rheumatic Ailments Increasing? There has been much discussion as to whether or not the actual morbidity rate is increasing. Sound figures on morbidity of chronic disease are hard to assemble. Many opinions regarding the occurrence of diseases affecting the heart and circulation have depended on mortality statistics. Such data do not help when one considers the large disabling group of rheumatic conditions. Rheumatism in its various forms is an infrequently reported cause of death. It is necessary in this group to rely on limited studies dealing with morbidity to arrive at an impression regarding its importance.

Simms reports [1] that the human death rate is lowest at the age of 10, approximately one death in 800 of the population. He shows that this rate increases 8 per cent each year throughout the life span. In 1936, approximately 1,300,000 deaths occurred over 10 years of age. At the 10 year rate, only 124,000 deaths would have occurred. Therefore, 90 per cent, or 1,-

* Read before the American College of Physicians, Annual Meeting, St. Paul, Minnesota, April 23, 1942.

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177,000 of the total, occurred because of an increase in the death rate with age. Simms considers that this depends on the underlying process of aging involving progressive alteration of the physiological function.

Simms further points out that 48 per cent of the total deaths which occurred in 1938 over 10 years of age were due to conditions affecting the cardiovascular or renal system.

In studying the vital statistics of the United States for 1939,[2] which have recently been released by the Bureau of Census, of the Department of Commerce in Washington, a computation of the deaths due to cardiac, vascular and renal conditions shows a total of 613,160 out of 1,387,897. Therefore, 44.9 per cent of the total deaths were due to these disorders. This figure differs slightly from that of Simms given above as it was calculated on total deaths rather than those above 10 years of age.

In considering similar data for the State of New York, which have recently been released in the vital statistics of the United States Department of Commerce,[3] it is apparent that there is an increase in the death rate from conditions associated with the vascular system. In 1935 the death rate per hundred thousand population was 481.3, and in 1939 it was 519.5. The death rate for all causes fell slightly from 1141.7 in 1935 to 1122.4 in 1939.

TABLE I

Death Rate of Selected Causes in United States, 1935–1939

All causes	Death Rates per 100,000				
	1939 1122.4	1938 1111.0	1937 1168.3	1936 1173.6	1935 1141.7
Intracranial lesions of vascular origin	74.0	71.9	75.6	78.9	76.3
Diseases of heart and blood vessels	375.4	359.9	356.3	347.5	325.6
Diseases of kidney (nephritis)	70.1	69.6	74.3	77.0	79.4
Total	519.5	501.4	506.2	503.4	481.3
Per Cent of Total	56.3	45.1	43.3	42.9	42.2

Another calculation from these data shows the frequency of death due to vascular disease in the later age groups, a fact which is generally known but which may not be emphasized with sufficient boldness. The death rate from heart, vascular and kidney conditions represented 50 per cent or more in all age groups over 60 years. In the age group from 50 to 60, it was approximately 43 per cent of the total deaths whereas in the younger age groups the proportionate number of deaths due to heart disease was much smaller.

In searching for data regarding the disability produced by rheumatic conditions, one is usually referred to the survey made in Massachusetts[4] where it appeared that the total number of patients disabled from rheumatic conditions was equal to or in excess of those disabled from heart or vascular conditions. In the National Health Survey of 1935–1936,[5] it was estimated

that rheumatic conditions affected 6,850,000 people of which 3,000,000 or more were considered to be due to arthritis alone. Rheumatic conditions are an outstanding cause of disability of a prolonged nature and of discomfort which may be well nigh unbearable.

If one looks no further than these two great groups of chronic conditions, namely cardiac, vascular and renal diseases and rheumatic ailments, there are in excess of 15,000,000 people in this country who have some de-

TABLE II

Number of Deaths, Selected Causes by Age, 1939

Years	All Causes	Intra. Vas. Les.*	Rheu. Dis. Ht.†	Coronary	Heart Other	Nephritis	Total	Per Cent
Totals	149,501	9,858	3,403	11,249	35,353	9,340	69,203	46.3
0– 4	8,906	23	15	2	39	22	101	1.1
5– 9	940	4	58	1	24	15	102	10.9
10–14	958	9	138	—	38	33	218	22.8
15–19	1,547	18	155	2	59	39	273	17.6
20–24	2,110	14	173	7	53	68	315	14.9
25–29	2,683	43	223	21	99	89	475	17.7
30–34	3,269	44	246	61	153	138	642	19.6
35–39	4,368	106	248	198	287	170	1,009	23.1
40–44	6,188	223	264	471	649	299	1,906	30.8
45–49	8,793	389	340	837	1,139	463	3,168	36.0
50–54	11,596	631	287	1,161	2,141	612	4,832	41.7
55–59	13,433	792	213	1,460	2,884	713	6,062	45.1
60–64	15,677	1,134	230	1,647	3,897	994	7,902	50.4
65–69	17,669	1,455	199	1,821	5,053	1,242	9,770	55.3
70–74	17,497	1,649	206	1,527	5,710	1,378	10,470	59.8
75–79	15,439	1,554	180	1,091	5,564	1,329	9,718	62.9
80–84	10,833	1,076	151	628	4,354	1,019	7,228	66.7
84–89	5,355	508	58	242	2,254	520	3,582	66.9
90–94	1,778	153	17	62	759	163	1,154	64.9
95–99	379	28	2	8	167	29	234	61.7
Over 100	61	5	—	—	28	5	38	62.3
Not stated	22	—	—	2	2	—	4	18.2

* Intracranial Lesions of Vascular Origin.
† Rheumatic Diseases of the Heart.

gree of disability from them. Of course, many are able to carry on their work and are self-supporting but large numbers are limited in their ability to support themselves and, therefore, present a large medical and social problem.

B. Is This a Problem of Senescence? Information is being assembled to determine what part various factors in the problem of aging have to do with the findings presented above. Stieglitz [6] has pointed out that gerontology may be divided into three major categories:

(1) The biology of aging
(2) The clinical problems of aging man
  (*a*) Normal senescence and senility
  (*b*) Diseases of the senescent period
(3) The social and economic problems of aging mankind.

In considering these categories, Stieglitz states that of all the diseases characteristic of later life, the cardiovascular group, including hypertensive arterial disease and arteriosclerosis, is by far the most prevalent in the senescent. He also stresses the fact that arthritis produces an immense toll of disability although its mortality is low. He points out that the maintenance of health, which is dependent on the mode of living, type of work, adequate sleep, type and character of exercise, utilization of leisure, as well as the correction of defects, is of vital importance to the aging individual. Diets are likewise essential, particularly with relation to total food volume, minerals, vitamins and fluids. He also points out the primary objective of prophylactic geriatrics is not only the prolongation of life but the insurance of greater health, vigor and usefulness for those past the meridian. Piersol and Bortz [7] have expressed this idea in cogent terms: "It is for science not only to add years to life; but, more important, to add life to years."

C. Ten Years' Spa Experience. The data presented are sufficient to indicate the scope and extent of the problem of the care of chronic disease in this country. No panacea has been discovered for the large group of individuals who suffer from either chronic cardiovascular disorders or rheumatic disability. What can the physician offer for these patients?

The author for the past 10 years has observed the influence of spa treatment on many patients suffering from cardiovascular, rheumatic, and other chronic disorders. At the Saratoga Spa, the total number of treatments given from 1932–1941 is presented in table 3. Approximately a

TABLE III

Treatments Given at the Saratoga Spa from July 1932 to June 1942

July 1932–June 1933	95,098
July 1933–June 1934	108,840
July 1934–June 1935	100,471
July 1935–June 1936	126,672
July 1936–June 1937	146,544
July 1937–June 1938	144,618
July 1938–June 1939	135,880
July 1939–June 1940	135,298
July 1940–June 1941	127,630
July 1941–March 1942	117,913
Total	1,237,964
Estimated to end of year	12,036
Treatments for 10 year period	1,250,000

million and a quarter treatments were given during this 10 year period. Owing to the large seasonal influx, it has not been possible to establish complete registration figures for the total number of patients taking these treatments. Based on a balance between the patients who stay only a few days and those who remain for the full period of three to four weeks, it is estimated that the average patient takes 10 treatments. Therefore, approxi-

mately 125,000 patients have received treatment at the Saratoga Spa during the past decade.

In 1936 a survey was made of records of patients covering both the charity group at the Spa and the patients treated by private physicians and 6,315 patients were classified on the basis of their primary medical condition. The data obtained from this study are presented in table 4.

TABLE IV

Classification of 6,315 Patients Treated at the Saratoga Spa

Primary Condition	Records of the Saratoga Spa 1933–36		Records of Private Physicians		Total	
	No. of Patients	Per Cent	No. of Patients	Per Cent	No. of Patients	Per Cent
1. Heart and circulatory disorders, including variations of blood pressure	522	26.5	1,425	32.7	1,947	30.8
2. Rheumatic conditions, including arthritis, myositis, fibrositis and neuritis	714	36.4	779	17.9	1,493	23.7
3. Gastrointestinal ailments, including liver and gall-bladder	218	11.1	896	20.6	1,114	17.6
4. Nervous conditions, including both functional and organic disorders	200	10.2	333	7.7	533	8.4
5. Metabolic diseases, including diabetes, obesity, and glandular disorders	83	4.2	174	4.0	257	4.1
6. Skin diseases (non-infectious)	18	.9	115	2.6	133	2.1
7. Miscellaneous	87	4.5	112	2.6	199	3.2
8. No disease, including general debility	121	6.2	518	11.9	639	10.1
Total	1,963	100.0	4,352	100.0	6,315	100.0

Applying the data obtained in this survey to the total number of patients treated during the decade provides information on the number of patients in each group who have received treatment. Table 5 is a summary of this information.

TABLE V

Total Number of Patients, 10 Year Period, July 1932–June 1942

Primary Condition	Patients
1. Heart and circulatory disorders, including variations of blood pressure	38,500
2. Rheumatic conditions, including arthritis, myositis, fibrositis, and neuritis	29,625
3. Gastrointestinal ailments, including liver and gall-bladder	22,000
4. Nervous conditions, including both functional and organic disorders	10,500
5. Metabolic diseases, including diabetes, obesity, and glandular disorders	5,125
6. Skin diseases (non-infectious)	2,625
7. Miscellaneous	4,000
8. No disease, including general debility	12,625
Total	125,000

D. What Are the Results Observed in the Treatment of These Patients? Patients coming for treatment are advised to have one of the physicians in private practice outline the program while here. Medical care is provided for patients in the charity group. Physicians in private practice contribute time to the Clinic Service during the summer months. It has not been possible to assemble at a central point records of all patients taking treatment at the Saratoga Spa. Also, many have remained only a few days and, therefore, cannot be included in evaluating the results of treatment. In summarizing the results it will be necessary to quote from individual studies which have been made on representative groups of patients. The evaluation of the results of this treatment naturally depends also on the patient's progress after he returns to his home. These data are not available except in a relatively small group of the patients who return for treatment during a subsequent season.

In studying the response of the circulation to the naturally carbonated mineral baths of the Saratoga Spa, McClellan, Joslin and Maguire [8] reported in 1934 on the study of 102 patients, 41 male and 61 female, in whom the pulse rate and blood pressure were observed daily before and after the bath for the period of their treatment. Care was taken to allow the patient on coming to the bath house to rest for a period of 15 to 30 minutes until the pulse rate and blood pressure reached a constant level. Under these conditions it was found that the pulse rate of a large proportion of the patients reached a resting level between 65 and 75. Even under these conditions, 83 showed a reduction in the rate of the pulse after the bath, 17 showed no change, and in only two patients was there an appreciable rise in the pulse rate. When the pulse rate at the beginning and end of the cure period was compared, there was relatively little variation because, as noted above, most of these patients had pulse rates within the normal range at the beginning of the cure.

With reference to blood pressure, the records of 88 patients in the series were available for study. Of this group, 52 had initial blood pressures above 150 systolic. When the entire group was considered, the average changes from the resting level before the bath showed relatively little change. However, a more careful analysis of those patients whose blood pressures were elevated above 150 mm. Hg showed that 52 per cent demonstrated a change of more than 10 mm. Hg which was taken as a significant variation. The authors concluded that the response with definite changes in the level of the blood pressure was found in those patients in whom some nervous influence could account for the elevation. When definite sclerosis of the arteries was present, or when kidney changes were evident, the elevated blood pressure showed relatively little reduction as a result of the course of treatment. They noted, however, that even though the change in blood pressure was not marked, many of these patients experienced definite symptomatic relief and left at the end of their cure apparently in better physical condition.

In another study Dorrance and McClellan [9] observed with the Tycos Sphygmomanometer 44 patients in whom the pulse amplitude and blood pressure were determined in a series of tracings, including the upper arm, lower arm, and lower leg, before and after the mineral water bath. Ninety pairs of tracings were compared. In all but one patient there was a decrease in pulse rate which was typical as noted in previous studies. The blood pressure variation in this group showed approximately the same percentage of response as reported in the preceding section. Significant variations in pulse amplitude as determined by the height of the tracings were noted in a considerable number of these patients. The definite tendency toward increase in amplitude following the bath was more evident in the upper extremity than in the tracings made on the lower leg, and was also more striking when the comparisons were made of those patients in whom the amplitude in the lower leg was 2° or less. The increase in amplitude was more frequently noted if there was some initial constriction in the arterial tree. Constriction of this type may be due either to organic changes or to muscular spasm, or both. Where definite increase in the amplitude occurred, it would appear that muscular spasm was a definite factor as the change was less marked in those patients with obvious organic arteriosclerosis.

Stein and Weinstein [10] have recently reported that local carbon dioxide baths prepared by chemical generation of carbon dioxide in the water did increase blood flow in the extremities as indicated by a study of the skin capillaries, the surface temperature and plethysmographic measurements.

Clinical studies include a series of careful observations by Comstock, Hunt and Hayden [11] on 107 patients in whom the diagnosis of coronary disease had been made. In a considerable proportion of this group, one or more attacks of coronary thrombosis had occurred. The authors reported that in 96 of the 107 patients, material improvement was noted. This is based on increase in exercise tolerance and diminution in the number and degree of anginal attacks during the period of observation. In 13 of these the improvement was sufficiently marked to include them in a separate group. The observations on the 11 patients who showed no improvement indicated that two did not complete the régime, three had advanced myocardial damage, one had suffered from malignant hypertension for three years, one was senile, one suffered from luetic cirrhosis of the liver, and one having repeated anginal attacks would not coöperate with the program. In spite of these facts, two of this group reported improvement after returning home. With reference to their study of the roentgen-ray examinations, electrocardiograms and vital capacity, the authors stated that there was no marked change in the heart shadow as determined by the cardiothoracic ratio at the end of the treatment. In the electrocardiograms they noted T-wave improvement, which they described in no instance as striking, in 22 patients. There was a reduction in the P–R interval in 15 patients. The QRS complex showed no significant change. They found no material change in the vital capacity of the series of patients studied.

McClellan [12] in 1937 presented a review of the physiological studies of the carbon dioxide bath. In general the observers have found that the physiological effects of these baths include a decrease in the pulse rate, an increase in the pulse pressure dependent mainly on the drop of the diastolic, the better emptying of the venous circulation, peripheral hyperemia with increased capillary circulation in the skin, a slightly elevated minute volume output of the heart, an increase in respiration, and the elimination of large quantities of carbon dioxide from the lungs.

The author pointed out that circulatory patients with mild to moderate myocardial weakening represent suitable indications for this program of treatment. Also, the patients with coronary sclerosis including the angina of effort, generally respond to the program. In the treatment of vasospastic conditions, with changes in the peripheral circulation, the bath is indicated as relaxation is frequently obtained during and after its use.

Definite contraindications to their use cover any cardiac patient with fever or active infection. Patients with luetic aortic regurgitation and aortic aneurysm generally show little benefit. Patients with advanced myocardial failure who require strict bed rest are not suitable for spa treatment.

In considering the results of treatment in other types of chronic diseases, the author [13] has reviewed the regimen with reference to rheumatic conditions. Many patients with osteoarthritis, as well as nearly all patients with fibrositis or myositis will show improvement with the regimen of treatment at the Spa. Patients with rheumatoid arthritis in the acute or active stage generally do not respond well to this treatment. Here the program includes the warmer baths with the local application of either hot mineral water or mud compresses, radiant heat or the infra red lamp, and it may include exercises and massage. For the rheumatic patient, this program offers considerable promise of relief, although it can in no sense be considered as the only form of treatment which should be used for these patients. It can be applied in conjunction with the general regimen now widely approved for these disabling disorders. In observing these patients during the cure régime, results obtained include a decrease in the swelling and increase in the range of motion of the affected joints. There is an improvement in the general physical condition of the patient which is manifested by better color of the skin, better elimination through the intestinal tract and kidneys, and a better attitude toward the disability which is present.

Convalescent care which has received considerable attention during the past few years can be satisfactorily associated with a spa program of treatment. Comstock [14] outlined this phase of spa work at the 1939 Conference on Convalescence at the New York Academy of Medicine. Callahan [15] has reviewed similar data with reference to the convalescent patient. They point out that a proper program of convalescent care in many of the disabling conditions is of real value in their continued well-being and from the standpoint of preventive medicine it may result in delaying the progressive development of the condition. Convalescent care also is applicable in the

building-up period after the occurrence of debilitating infection or a weakening surgical operation.

Summary and Conclusions

1. Chronic disease in middle and old age is a serious medical problem in this country.

2. Lack of attention to matters of health in earlier years may be one contributing factor to the development of these chronic conditions in the older age groups.

3. No magic drug or miraculous fountain of youth has been discovered for these conditions.

4. Much investigation in the field of geriatrics is under way and it is hoped that this will be productive of information which will aid in the regulation and control of these conditions.

5. Spa therapy can be utilized to advantage for selected patients with chronic ailments such as cardiovascular, rheumatic, gastrointestinal, metabolic, and skin disorders. It can be fitted into the physician's schedule for the chronic patient but he must know its indications and contraindications.

6. The facilities available at the spas can also be used in the convalescent care required after acute illness or injury. Thus they have their place in the field of industrial and military medicine.

7. In addition to the use of the natural agents which is the keystone of the program, rest, regulated exercise, diet control and proper recreation all have a part to play in producing the desired mental and physical relaxation.

8. In order for the patient suffering from chronic disorders to derive the maximum benefit, it is necessary for the home physician to select the proper spa for his patient, taking into account the natural facilities available, the climatic factors and the availability of adequate medical control.

9. Long-term observation of groups of patients with chronic diseases, who have received treatment at spas will be required to determine finally how completely effective the program may be.

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CIRCULATORY DISTURBANCES IN PROSTATIC HYPERTROPHY *

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A REVIEW of the medical literature reveals the fact that but little consideration has been given the very important relationship of the hypertrophied prostate to circulatory disturbances. Perhaps it has been assumed that persons of the age to have hypertrophied prostates should have certain cardiac and circulatory changes as a natural sequence of old age. As we live in a section of the country which has a large influx of elderly people during a portion of the year, the opportunity of observing the diseases of advanced years is greater. Also, owing to the fact that people from nearly every part of the country are here at least a short while, methods of treatment in other sections can be clearly observed.

To the majority of diagnosticians, the patient with the cardiovascular-renal syndrome still represents a poor surgical risk. Operation is often deferred or, in many instances, abandoned completely because of the chances involved, with the result that a large percentage of patients with prostatic disease are denied timely relief through surgery because of the co-existing cardiovascular disturbance. After establishing the cardiac functional capacity or incapacity of the patient, a great number of urologists feel that, in cases of advanced myocardial incompetence, suprapubic cystostomy or catheterization should be resorted to as the only means of relieving the urinary obstruction.

There is no question but that there is a general tendency to treat prostatic hypertrophy too conservatively because of the existing evidence of some degree of circulatory failure. The next question is whether or not the circulatory disturbances are the result of, or at least aggravated by, the presence of an incompletely emptied bladder. It would seem that either the retention of nitrogenous products in the blood stream or some reflex action upon the excretory function of the renal units has a definite effect upon the circulatory system. Campbell [1] advances the theory that hypertension occurs in a small group of prostatic patients because of the inability of the upper urinary tract to dilate owing to an anatomic factor, usually an intrarenal pelvis, and he points out the strikingly low rate of hypertension (19 cases) among the group of 173 cases of prostatism studied by him.

The final decision as to surgical intervention depends, in many instances, on the condition of the heart and vessels. The responsibility is left by many urologists upon the shoulders of the internist or cardiologist, and too often

* Presented at the Annual Meeting of the American College of Physicians, April 21, 1942, St. Paul, Minnesota.

the opinion is that the patient is not able to undergo surgical interference. Many allow their patients to die with their hypertrophied prostates rather than take the risk of removing the obstruction which, in practically all cases, will help to improve the circulation. This fact can be effectively demonstrated by doing suprapubic drainage on the very poor risks before attempting resection or even prostatectomy.

No definite criteria or rules as yet can be laid down relative to the laboratory procedure which would indicate when it is safe to proceed. The decision must be based largely upon the clinical judgment of those who have had the opportunity of studying many cases. Laboratory findings and functional tests are empirical at best, and it is impossible to formulate any one into any safe rule which could be followed. As an example, in the series of patients to be presented the blood urea nitrogen varied from a low of 10 to a high of 31 milligrams which is certainly no evidence of impending danger. The blood pressures ranged from a systolic of 70 mm. Hg and a diastolic of 50 to a systolic of 220 and a diastolic of 110.

That the inter-relationship between renal dysfunction and cardiac impairment is clearly recognized is shown by Thompson.[2] In a study of a large series of patients subjected to prostatic surgery at the Mayo Clinic, recognized heart disease was found in 23 per cent on admission and 28 per cent showed blood pressure readings above 160 millimeters of mercury.

Among the cardiac symptoms complicating the prostatic hypertrophy were auricular flutter, auricular fibrillation, myocardial decompensation, rheumatic heart disease, angina pectoris, and hypertension. These patients ranged from 65 to 80 years of age. Forty-eight per cent had a systolic blood pressure above 150 and the average blood pressure in this group was 179.5 systolic and 100 diastolic. On discharge from the hospital after relief of the prostatic obstruction the average blood pressure had fallen to a systolic of 140 and a diastolic of 80.

Preoperative strengthening of the myocardial reserve is the essential step in lessening the hazards of major surgery. The failing heart muscle in the case of prostatic obstruction should be treated as any other case of cardiac failure. Complete rest is the most important therapeutic agent and with this must be relief from frequent or difficult passing of urine. Digitalization should be begun at once and continued until after the shock of the operation is over. As many of these cases show some degree of avitaminosis, the administration of vitamin B complex is strongly advocated. This is better done by the intravenous injection. Anemia is present in many cases and should be treated during the preoperative period. The preoperative period must not be curtailed or hurried.

Elevation of blood pressure should not constitute a contraindication to surgery. Wilhelmi [3] has recorded the case of one patient with a systolic blood pressure of 240 who had four resections without reaction at any time, and another with hemiplegia and a systolic pressure of 210 who underwent two resections with no ill effects. Although Seng [4] stresses the pos-

sibility of any catastrophe occurring in the hypertensive prostatic patient because of the condition of his cardiovascular system, he, as well as O'Conor [5] and others, has demonstrated the marked fall of blood pressure following the relief of chronic urinary retention. O'Conor recorded that the blood pressure in 75 per cent of hypertensive patients reached its lowest level in 48 hours after the institution of continuous catheter drainage.

Cutler [6] stresses the point of preoperative study and care of patients in general, and emphasizes that the elderly will always require a longer period of preoperative observation and a more accurate study of end results than other groups. In connection with this Cutler states: "The ideal considerations surrounding a satisfactory surgical risk permit the patient to come to operation with the tissues adequately supplied with fluid, the food reserves in their normal state, the metabolism adjusted as perfectly as it may be, the intestines working normally, the circulation at its optimum level, and a nervous system as undisturbed and peaceful as in daily life."

Levine [7] enumerates a series of surgical patients suffering from various types of heart disease. In the group with marked valvular disease only 2.1 per cent of the deaths followed the surgical procedure, whereas among the patients who showed non-valvular cardiac involvement (hypertension, chronic myocarditis, etc.) there was a mortality rate of 4.9 per cent.

Mortality rates as shown by one of us * vary with the experiences of the operator. It was noted that five urologists, who had operated upon more than 500 cases each, had a combined mortality of 1.9 per cent in 4,767, whereas 25 who had done between 100 and 200 resections had a combined mortality of 4.1 per cent in 3,530 cases. It is obvious, therefore, that morbidity as well as mortality have been greatly lessened by the experienced resectionist. Immediate postoperative shock has been practically eliminated and many patients who represent a surgical risk may at present be given timely relief from their distress.

Thompson and Habein [9] claim that the choice of transurethral prostatic resection has materially reduced the immediate postoperative mortality rate, formerly encountered as a result of suprapubic and perineal prostatectomies, by 90 per cent. Even patients belonging to the advanced age groups, who suffer from serious cardiovascular-renal disease and other degenerative impairments, tolerate this form of surgery without ill effects. These two authors have also analyzed the histories of 1200 patients 70 years old or more, who were operated upon prior to January 1, 1938. Some of these surgical candidates had submitted to two, and in a few instances, to three operations, making a total of 1,361 transurethral resections.

In comparison with the figures quoted above, which include all surgical patients, 29 cases have been selected that gave either a history of active myocardial failure or a history of recent myocardial infarction. All were advised to have surgical interference for their urological condition. The degree of cardiac involvement varied, but as a whole they were those cases

* Dr. Louis M. Orr II.[8]

that are very often advised not to undergo surgery. Two of these patients had had coronary occlusion but had recovered. The remainder all had signs of a failing myocardium and in some there was a history of previous attacks going back one to eight years.

The ages of the patients in this series varied from 55 to 83, the average age being 71 years. Of this series seven have died, i.e., a percentage of 24.1. One died one year after the operation. Another died seven months after surgical interference and the urological condition of this patient was complicated by diabetes mellitus and, previous to the operation, by the presence of a bundle branch block which later disappeared. There was a period of fair circulatory balance following the operation; however, the seriousness of his condition could not be impressed upon him and a few months following operation a long motor trip was undertaken which brought on circulatory failure for which no relief could be given. A third patient died three months after leaving the hospital. He was uncoöperative even in the hospital and after returning to his home in a neighboring county no supervision was possible. Two died of circulatory failure the day following resection, and another death occurred in the case of a diabetic whose blood sugar could not be controlled following operation and who presented considerable liver damage. The seventh died of bronchopneumonia five days after the resection.

After taking into consideration the various complications, it can be said that only two patients who had signs of circulatory failure previous to admission actually became worse immediately following the operation. One of them had suffered from bronchiectasis for a number of years. This is a percentage of 6.8 which is only three to four times the mortality record of all cases considered in the various series presented. The patients of this series definitely belong to the class which undoubtedly would have succumbed early to circulatory failure had they not been given a chance for a little borrowed time through surgical interference.

Hypertension was present in eight cases previous to the operation and on discharge from the hospital the pressure was within normal limits. In the 29 cases the average length of stay in the hospital before any surgical procedure was undertaken was 11.5 days. The average postoperative stay at the hospital was 10.4 days, with an average total of 21.9 days of hospitalization. Of this series four patients had suprapubic prostatectomies, and two others had suprapubic prostatectomies following resection.

In only four cases were the laboratory data indicative of a nitrogen retention, so that this factor can be eliminated as a cause of failing circulation. An important factor which is seldom mentioned is the stress and strain associated with the frequency and marked exertion during urination. This straining must be a definite factor in the circulatory failure for it will be noticed that a cystotomy or an indwelling catheter will usually bring on more or less relief to the heart muscle. Bed rest was not the factor that was necessary for the cardiac improvement for many of these patients were not

confined absolutely to bed. It can definitely be said that all except those mentioned showed great improvement following their operation.

The following case may serve as a concrete example. This patient was seen in 1935 at the age of 63, when examination revealed myocardial damage. He was in bed for several weeks and was seen in consultation by two internists who both considered him to be near the end. He was treated intermittently; in 1937 an electrocardiogram showed coronary sclerosis had developed; and in 1938 a posterior coronary occlusion with accompanying muscle damage complicated the clinical picture. The patient also had trouble with urinary retention. By 1940 he had dropped all work and activities owing to his aggravated heart condition and he began to complain of difficulty in emptying the bladder in the morning. There was no increased frequency during the day. The patient was finally admitted to the hospital in October, 1940. At the time of his admission he complained of increased urinary difficulty. Physical examination revealed an enlarged prostate, a moderately enlarged heart with a soft blowing systolic murmur at the apex. Blood pressure was 110 mm. Hg systolic and 70 mm. diastolic. An electrocardiogram showed myocardial damage, extraventricular systoles, coronary sclerosis and a posterior infarction.

The operative procedure was carried out under local anesthesia (spinal pontocaine) and consisted of bilateral vas ligation and prostatic resection, both manipulations requiring a total of 50 minutes. Approximately 11 grams of tissue were removed. A No. 24 Foley catheter was used. Complete and final diagnosis in the case of this patient was: carcinoma of the prostate, arteriosclerotic heart disease, coronary sclerosis and occlusion with mitral insufficiency. Regardless of these four serious complications the patient stood the operation remarkably well and made an uneventful recovery. He was allowed out of bed on the fourth postoperative day and was dismissed on the ninth day after surgical intervention. He has returned to his normal activities and periodic examinations have revealed no complications of any kind. This, as well as the majority of patients who had cardiovascular complications and were subjected to prostatic surgery, showed decided and most remarkable improvement of all clinical symptoms. Normal function of the circulatory system was restored as soon as the obstruction caused by the hypertrophied prostate was removed.

The choice of a proper anesthetic is of primary importance in the surgical treatment of these patients. It should be easy of induction, provide adequate pain relief, be rapidly eliminated from the body and reduce gastrointestinal, pulmonary, and circulatory complications to a minimum. Although the ideal anesthetic has not as yet been discovered, it is felt that pentothal sodium given in conjunction with oxygen and administered by a capable anesthetist most clearly satisfies these requirements for the cardiac case.

Infusions of plasma or whole blood should be a part of the routine postoperative treatment in severe cases. The most speedy and skillfully per-

formed operative manipulation fails to avoid a serious loss of blood which must be replaced promptly if shock is to be eliminated. It is probable that the loss of blood will average in the neighborhood of 300 to 400 c.c. According to Gundersen [10] 70 per cent of his patients who were studied in 1937 received one or more blood transfusions. In these cases heart disease claimed only two patients one year after leaving the hospital.

An attempt has here been made to evaluate the favorable and unfavorable conditions associated with obstructing prostatism and to determine the advisability of prompt surgical interference in spite of an impaired cardiovascular system. It is a fact that prostatic patients of the old age group who several years ago would have been rejected as too great surgical risks because of advanced senility or serious cardiac defects, are today being treated by means of resection with excellent postoperative results and, as has been shown herewith, decided improvement of the failing heart muscle. Mortality rates in prostatic surgery can and will be greatly lessened by a careful surgical approach to the problem which must be based upon preliminary preparation of the patient.

Summary

1. Cases of hypertrophied prostates showing signs of active circulatory failure are, generally speaking, to be considered fair surgical risks.

2. The removal of the obstruction to the urinary outflow aids greatly in the improvement of the cardiac condition. The exact reason for this is as yet unknown.

3. Failure to operate on these cases only aggravates the condition of the heart.

4. Proper preoperative and postoperative treatment will result in a reduction of the mortality rate to a level comparable with the most favored surgical risks.

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SOME PROBATIVE ASPECTS OF THE EARLY GERMANIC CODES, CAROLINA AND BAMBERGENSIS *

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In February 1533, a document of unique historical importance was struck on the press of Ivo Schöffer, a printer of Mainz. As though foreshadowing its ultimate obscurity in English speaking countries, this prototype of scientific-legal proof was indifferently received and inattentively handled from its inception.[1] Enacted as a statute a year earlier by the Reichstag at Regensburg under the imposing title, "Kaiser Karls des fumfften und des heyligen römischen Reiches peinlich Gerichtsordnung," it is perhaps better known as the Carolina Code, or the Penal Laws of Chas. V.[2]

Earlier in the 1500's had appeared another code, the Bambergensis. This work, composed in large measure by Johann Freiherr von Schwarzenburg, served as a model and foundation of the criminal law of Germany for approximately four centuries. That it profoundly influenced the Carolina Code is patent from the striking similarities in form and content between them. Article CXLVII of the Carolina Code is, for example, paralleled almost word for word by Article CLXXIII of the Bamberger Code.[3] In geographic scope, however, the Carolina was by far the broader code. Its jurisdictional effect was nationwide, whereas the Bambergensis (and also the Brandenburg code) represented local law only.

I. Anglo-Saxon Underestimation of the Codes' Significance. The neglect of both these tracts in the English-speaking world during the past century may be attributed in part to the disproportionate harshness of the system of punishments they expostulate. The rude community life of renascent Europe did not regard burning, drawing and quartering, breaking on

* Received for publication March 9, 1943.

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[1] Von Bar, *History of Continental Criminal Law* (1916), p. 44, points out that not a single copy of the original was retained by the imperial officials and that there are enough errors in the writing and editorial work of the original draft as well as in the typography of the principal edition of February 1533, so that frequently it is difficult to ascertain the meaning. There is also, according to that authority, some dispute as to the existence of earlier editions.

[2] *Constit. Crim. Car V.* ed. J. F. Ludovic, Halle 1716. Further references to this code are by way of our own translation from the original German.

[3] Article CXLVII of the Penal Laws (Carolina Code) and Article CLXXIII of the Bamberger Code are identical except for (1) punctuation and spelling, the Bamberger Code being written apparently in older German, (2) the addition in the Penal Laws of the words "and the fracas" (*"und Rumor"*) after the word "blow" and before the words "and how long he lived after he was 'struck,'" and (3) the more formal ending of the Article of the Penal Laws which concludes, "and the judge shall, in accordance with his understanding of the law, and the authorities and purpose of the law, and the purpose of this enactment, give due consideration to such testimony."

the wheel or rack, pinching with hot tongs, or burying alive as particularly inhuman or barbaric. It is not surprising, therefore, to find such punishments incorporated in both codes. These codes were intended as treatises limning the law as they found it, with the greatest degree of clarity possible, rather than statutes of legislative reform. Nor is it strange that the same cruelties were reflected in the use of torture as a means for determining the truth.

It is not difficult to overlook primitive methods of punishment in a work not primarily concerned with penal reform nor with modifications in the severity of corporal punishment. Such leniency cannot be condoned when these same tortures are a matter of procedure in an exposition chiefly procedural and concerned with rules of proof. Perhaps this fact has blinded able legal historians to the full importance of the Carolina and Bambergensis as almost aboriginal harbingers of an era of scientific-proofmaking of which only the van has arrived even today. External evidence had already contrived even at that early age to influence that least objective of all probative tests, the rack. Thus Article LIX of the Penal Laws (Chas. V) and Article LXXII of the Bamberger Code provide in identical language for excusing a defendant from torture (the rack) so long as he has dangerous wounds or bodily injuries.[4]

In the interval between promulgation of the Bambergensis and the Carolina, the former code had already achieved recognition as authoritative. Thus in 1516 it was adopted with relatively few changes as the code of the margravate of Brandenburg. By the time of the Carolina, the strong sympathy of the earlier codes toward objective evidence in the form of expert testimony had sufficiently permeated legal thought so that express provisions of this character were added where none had expressly existed before. Thus, for example, we find no section in either the Bamberger or Brandenburg code to parallel Article CXLIX of the Penal Laws (Carolina), "of the Inspection of the Body of a Slain Man Before Burial."

> Where there is reason to believe that there has been foul play, the judge shall have the clerk of the court and one or more surgeons carefully inspect the dead body before burial, and carefully observe and record all the wounds, bruises and swellings that they find.[5]

[4] The *Note to Article LIX* says that epileptics are a hard problem; and cites Brunnem, *proc. inquis.*, c. 8. membr. 5. n. 28. seq., to the effect that the opinion of a physician should be consulted before judgment is given, and that the judgment should conform to the physician's opinion as to what kinds of torment, if any, the men are subject to; and also cites Carpzov, *prax. crim. qu.* 118 num. 18 and 19, to the effect that physicians should be consulted as to whether epilepsy is really present or the fits are simulated.

[5] The *Note to Article CXLIX* conjectures that the inspection need not be made in the presence of the judge. It adds that the corpse may sometimes be exhumed, if it was buried without previous inspection and putrefaction has not yet set in.

Citation of B. Stryk, *de jur. sens. diss.*, 1 c. 2. num. 34, who wrote that surgeons were altogether prohibited from exploring a wound, before the cadaver had been dissected, with any kind of iron instrument, and from probing or cutting any interior part of the body. The reason given was the censure of physicians who were summoned to inspect corpses on which surgeons had already worked with iron instruments. For the more surgeons tamper with the bodies, the less the physicians themselves can draw inferences from their inspections.

II. Evaluation of the Codes. It must not be imagined that the Carolina, and, a fortiori, the earlier codes, are in any sense a complete and objectively consistent system of scientific proof. Even in their most detailed sections concerning the elements of objective proof-making, important girders are missing in the superstructure of evidence. These gaps may be traced, however, to philosophical inadequacies rather than fallacies in logic. The Code Carolina is internally harmonious with respect to its reasoning. Its deficiencies are philosophically and psychologically inherent in the culture of its period, a period that believed that the only positive proof of crime was confession[6] and that torture was merely an instrument of confession. Although sections LXIX and XXII of the Carolina prohibited any conviction upon circumstantial evidence, judicial interpretation soon limited the prohibition to the graver offenses. And even here the technical requirements of confession or eye-witness testimony were speedily ignored. Where the judge was convinced of the actual guilt of the defendant, he sentenced him to *Verdachstrafe* ("extraordinary" or as later known, "suspicion" punishment). The lay feeling against external or circumstantial evidence, uncorroborated by confession or eye-witness testimony, merely shifted the method whereby the ultimate end was achieved. The judiciary which recognized the value of circumstantial proof assumed the power to effectuate and express that recognition in punishment, despite the provisions of the Carolina. Seen in proper perspective the Carolina channelized much of the incipient law of scientific proof, but was itself only a part of a much broader stream flowing in the same direction.

III. Comparative Analysis of the Codes. Comparative analysis of a particular problem in probative valuation in both codes may more readily illustrate their differences and salient strengths. Particularly apt are Article XXXVI of the Penal Laws (Carolina Code) and Article XLIV of the Bamberger Code concerning the proof-standard for maternal infanticide. The earlier (Bamberger) code provided:

> But if the baby has been killed so recently that the milk in the breasts of the mother may not yet be gone,
>
> and the woman who is blamed asserts that she is a virgin,
>
> then her breasts shall be milked, and if milk is found in the breasts, she must necessarily have had a child and shall be put to the torture (for questioning).

In the asset column of the code may be listed the clear formulation of a test in language simple enough for the lay mind to grasp, and the execution of the test by those especially qualified to attest the significance of the results, as well as the results themselves. As undeniable weakness of the article, on the other hand, is the rigidity of the test, not making allowances for possible differences of medical opinion. The Carolina Code corrects this obvious de-

[6] See von Bar, *History of Continental Criminal Law* (1916), p. 52. Also cf. the prejudice of the lay mind of today toward circumstantial evidence as the sole instrumentality of conviction in capital crimes.

fect by changing the absolute conclusion of the law to a strong presumption rebuttable by sufficient weight of expert testimony. A glance at the Penal Laws of Chas. V strikingly reveals the difference.

> If the baby has been killed so recently that the milk in the breasts of the mother may not yet be gone, then her breasts may be milked, and if milk is found to come readily from her breasts, there is a strong presumption against her that she should be questioned under torture. But since several court physicians say that from various natural causes a woman who has borne no child may have milk in her breasts, therefore when a woman in this situation tries to excuse herself accordingly, further experience, that of midwives and others, shall be consulted. [7]

Had the early Germanic codes rested their case at this point, their conceptual similarity to the spirit of the modern idea of scientific proof-making would have been even more striking. Unfortunately, in the serious crimes, circumstantial evidence alone was considered insufficient. As has been pointed out before, the judiciary frequently by-passed this hurdle through "suspicion" punishment (i.e., punishment based on sufficient circumstantial data to satisfy the judge of the actual guilt of the accused, despite lack of a confession or eye-witnesses). Still, the codes themselves are undeniably weakened as models, even early models, of the law of proof by such provisions as Article XXXV of the Penal Laws, and Article XLIII of the Bamberger Code. These articles concern the circumstances on suspicion of infanticide. Yet even here the directional urge toward scientific standardization is manifest, at least to the extent of determining the primary issue of still birth versus death after birth. The *Note* to the articles mentioned, asks:

> What shall be done when an infant is found killed?

. . . The question whether the infant was born alive is submitted to medical opinion . . .

> First examine the lungs to see if they are red and bright, and throw them without bruising into a kettle of water; then if they *float,* "that is a certain and infallible sign of a child born alive, according to the opinion of all physicians and anatomists." (Authorities cited.) If, on the contrary, the lungs *sink,* that is a sure sign that the foetus was dead in the womb, and never breathed.[8]

[7] The *Note* remarks that no appeal to expert evidence is provided for in either the Bamberger or the Brandenburg Code, since at the time when they were formulated the milking test was considered infallible. Considering the close spacing of the various codes (Bamberger 1507, Brandenburg 1516, Carolina 1530–32), this explanation with respect to the omission may be open to some question. But even if accepted at face value the importance of the procedural difference between the earlier codes and the Carolina remains unaltered from the standpoint of objective standards of expert testimony.

[8] Pp. 50–51. The note then refers to a commentator, B. Beyer, who pointed out that the test works well with a fresh cadaver, but not with a cadaver that has had time to putrefy, since putrefaction generates gas. See, also, Article CLXXIX which provides for insanity to be taken into account in fixing the punishment for crime and specifies that expert witnesses may be heard on that issue. In the note to this article a case is reported where the verdict of the court in a case of alleged mental irresponsibility was based upon the expert opinion rendered by the Medical Faculty of the University of Halle (1706).

Article CXLVII, of the Penal Laws, although not specifically concerned with infanticide, embraces that problem under the general heading, "When someone has been struck, and dies, and there is doubt whether he has died of the wounds. . . ." In such a case, the parties may introduce the testimony of the attending surgeon, and of other persons familiar with the facts, as to whether the deceased remained standing after the blow, and how long he lived after he was struck; and the judge shall give due consideration to such testimony. The important factor to be noted is that the medical inferences of the attending surgeons are placed on the same plane with the testimony of other persons familiar with the facts. That this is due to a clearly defined regard for principles of scientific proof and not a cultist psychology of science-worship is evidenced by the *Note* to the Article. This *Note* "informs us that surgeons by themselves are hardly trusted, but that in practice a physician is summoned at the same time." [9]

[9] Also see citation of B. Stryk, *de jur. sens. diss.*, in footnote 5.

CASE REPORTS

AMYLOIDOSIS IN CHRONIC ATROPHIC ARTHRITIS*

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Since amyloid infiltration was first brought to the attention of the medical profession by Rokitansky and the Viennese school only a few cases of amyloidosis associated with chronic arthritis have been reported. This relative sparsity of reports prompts the discussion of the following case.

Amyloidosis most frequently complicates tuberculosis and other diseases in which chronic suppuration occurs, such as osteomyelitis, pulmonary abscess, pyelonephritis and others. Certain chronic diseases which lack obvious suppurative processes but have occasionally shown amyloid deposits are Hodgkin's disease, cirrhosis of the liver, leukemia and myeloma. Amyloidosis has been found also in nonsuppurative infectious diseases such as syphilis, malaria, lymphogranuloma and chronic atrophic arthritis.

A few reports have appeared in the more recent literature of the presence of amyloidosis in association with chronic arthritis. Schneiderbauer,[1] Hardgrove[2] and Reimann and Eklund[3] cite cases of typical atrophic arthritis; Moschcowitz[4] had two cases, one with atrophic arthritis and another which would be classified as infectious arthritis. Lengh[5] reported one case of septic polyarthritis in which a renal infection was thought to have been the cause of the amyloid disease. Imrie and Aitkenhead[6] had one patient and Portis[7] had two patients who developed amyloidosis in the course of Still's disease (chronic atrophic arthritis of children). The patient of Koletsky and Stecher[8] presented symptoms of chronic arthritis over a period of 14 years and at autopsy there was extensive amyloid involvement of the joints, bones and other structures. They classified this case as primary systemic amyloidosis. The patients reported by Feller,[9] Michelson[10] and Perla and Gross[11] are cases of primary amyloidosis in which arthritis was present. In these cases the amyloid was probably primary and in no sense a complication of the arthritis.

The importance of amyloidosis in chronic atrophic arthritis concerns its etiology. Many theories have been proposed for the presence of amyloid infiltration, but those factors which might be considered in the discussion of atrophic arthritis are the disease itself and the therapeutic use of parenteral injections. Without any attempt to review the already voluminous literature on the subject of amyloidosis the following case is reported.

Case Report

L. P., a white male, was first seen in the dispensary of St. Alex Hospital at the age of 36 years. He had no other illness except arthritis, which began when he was 30 years old and followed the clinical course of the more severe and rapidly disabling

* Received for publication January 30, 1941.
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form of chronic atrophic arthritis. When first seen the arthritic process had involved all the joints of the body. The vertebral column was immobile, with the neck fixed in 15° of flexion. There was severe deformity of both hands and wrists, and the fingers were ankylosed in approximately 45° of flexion. There was induration about the elbows, and limitation of motion. Both shoulders had only limited impairment of motion. The knees were enlarged and could not be extended completely. The toes were deformed, and there was bilateral hallux valgus. The temporomandibular joints were partially ankylosed. No joint was acutely inflamed. The patient, though handicapped with his deformities, had been about after a fashion with the aid of two canes. The clinical symptoms and signs did not change materially during the three years of his visits to the dispensary until just before his death.

Injections of Crowe's vaccine subcutaneously were started soon after his first visit. Crowe's vaccine is a stock vaccine made in Dr. H. Warren Crowe's Laboratory, London, and includes several strains of streptococcus and staphylococcus. These injections were given weekly during his three years' attendance at the dispensary and totaled 136. The amount of this mixed vaccine administered varied from 1000 to 15,000 organisms per week. For the first 26 weeks in addition to the Crowe's vaccine he received a weekly intravenous injection of colloidal sulfur 30 milligrams each or a total of 780 milligrams. The sulfur injections were discontinued, but he continued to receive the Crowe's vaccine until one week before his death. He received no drugs or any other therapy during these three years. Though his diet was not ideal, it was not obviously deficient.

Eight months prior to his death, he was admitted to the hospital for further study. The pertinent findings at this time were: the heart showed a questionable systolic murmur at the apex; there was marked atrophic arthritic involvement of every joint; the urine had a specific gravity of 1.017; albumin two plus; microscopic, many fine and coarse granular casts; red blood cell count 4,400,000; hemoglobin 13 grams; white blood cell count 9550; sedimentation rate 122 mm. in one hour (modified Westergren method); and the liver function test with iso-iodekon showed 5 per cent in 30 minutes and "too low to read" in one hour.

Shortly before his death he was readmitted to the hospital because of persistent vomiting and pain in the abdomen. At this time the examination disclosed: heart, systolic and diastolic murmur at the apex; blood pressure 146 mm. Hg systolic and 80 mm. diastolic; the abdomen was rigid in upper half, and there was dullness on percussion. Laboratory findings—urine, specific gravity 1.011; albumin four plus, microscopic, many red cells; red blood cell count 3,200,000; hemoglobin 12.5 grams; white blood cell count 10,000; sedimentation rate 117 mm. in one hour; blood urea nitrogen 180 mg.; uric acid 9 mg.; creatinine 6 mg. Soon after admission he lapsed into coma and died on the fourth day.

Autopsy Findings. Autopsy was performed by Dr. John L. Work four hours after death. The body was that of a severely deformed, moderately emaciated, asthenic white man appearing 5 to 10 years older than the stated age of 39 years. The deformities were those of chronic atrophic arthritis and were present in all the joints. The skin over the affected joints was tense, thin and shiny. There were shallow decubiti in the sacral region, and the skin and mucous membranes were pale. There was moderate edema of both lower extremities and the scrotum. The mouth was edentulous. More fat was present in the subcutaneous tissues than was expected from the external appearance of the body. It was pale lemon yellow and had the normal consistency.

The heart weighed 375 gm. Except for nodular thickening and calcification at the base of the anterior mitral leaflet, there was nothing noteworthy. The lungs were the seat of apical scars and severe edema and there was bronchopneumonia on the right side. No primary tuberculous foci were demonstrated. The liver

weighed 1975 gm. Its edges were blunt and its capsule was tense. The parenchyma was firm but friable. The cut surfaces bulged slightly and were dull reddish brown, shiny and translucent. The markings were hazy. There was cholesterolosis of the gall-bladder. The spleen weighed 140 gm. The cut surfaces were flat, reddish gray, and yielded very little blood or pulp when scraped. The adrenal glands showed no gross abnormalities. The right and left kidneys weighed 150 and 125 gm. respectively. The parenchyma of both was firm and peculiar, dull pinkish gray. The decapsulated surfaces were dotted with rosettes of tiny dilated blood vessels and punctate hemorrhages. There was slight bulging of the cut surfaces. There was a reduction in the thickness of both cortex and medulla and the ratio of the one to the other was reduced. The markings were indistinct or completely obscured and the cortices were studded with pearly gray dots. The pelves and calices were normal. There was no deformity of the thoracic or lumbar segments of the spine, but sections through the vertebral bodies showed abnormally thin cortices and delicate trabeculae. The bone marrow was pale pink and pultaceous.

Microscopic preparations revealed marked amyloidosis of the liver, spleen and both kidneys. The degree of involvement in the liver and spleen was much greater than their gross appearance indicated. In the liver the amyloid was present in the usual situation. In the spleen it was confined to the follicles. Sections through the kidneys showed lobulated collections of amyloid between the epithelium and the capillary endothelium of all glomerular tufts. The tufts were enlarged, bloodless and frequently fused with their capsules. The capsular epithelium was swollen and there was mild sub-capsular fibrosis. There was a reduction in the number of tubules and those which remained were dilated. There was diffuse fibrosis of the interstitial tissue and an infiltration of fibroblasts, lymphocytes, large mononuclear cells and varying numbers of eosinophiles and plasma cells. The arteries and arterioles showed no significant abnormalities. Small amounts of amyloid were present in the cortex of both adrenal glands.

The anatomical diagnosis was: chronic atrophic arthritis; amyloidosis of the kidneys, liver, spleen and adrenal glands; edema of the lungs, marked; and bronchopneumonia.

Comment

The patient is a typical case of atrophic arthritis. The disease was sufficiently severe to cripple him in relatively few years. The disease was definitely chronic with clinical and laboratory evidence of a low grade infectious process. There was no suppuration either grossly or microscopically. Thus none of the conditions ordinarily associated with the deposition of amyloid were present in this case, yet in distribution and character it was characteristic of secondary amyloidosis. The tuberculosis in the apices of both lungs was slight and anatomically healed, and the changes in the kidneys appeared to be the result rather than the cause of the amyloid. Consequently, from a combined clinical and anatomical standpoint the likely causes of the amyloidosis are the chronic atrophic arthritis itself, the vaccine therapy, or a combination of the two. If chronic atrophic arthritis alone causes amyloidosis, it is difficult to explain the fact that so few cases have been reported. It is doubtless true that comparatively few patients with atrophic arthritis die in those hospitals in which autopsy permission is actively sought. During the past 24 years there were only six autopsies in a total of 15,000 available autopsy records in which a diagnosis of chronic atrophic arthritis was made, and in none of these was there amyloid in any structures. Certainly the autopsy records of the average hospital, in this city at least, fail to

indicate the true incidence of chronic atrophic arthritis in the general population. However, even though so few cases are seen at autopsy, it would seem that if amyloidosis were present more frequently in this relatively common disease, it could be confirmed by the adequate clinical signs and laboratory tests which are now available.

The factor of vaccine therapy should be considered. For a period of three years the patient received weekly parenteral injections regularly and frequently, missing only 17 injections in a total of 168 weeks. The vaccine used was made from streptococcic strains, which are thought to be more potent factors in the production of amyloid.

Reimann and Eklund [8] reported a case of a patient with chronic atrophic arthritis who received 41 injections of a streptococcus vaccine intramuscularly and intravenously over a period of 22 months. They came to the conclusion that "because of the rarity of the occurrence of amyloid disease in chronic arthritis and the frequency with which it occurs following long continued parenteral injections of numerous substances including vaccine, it was believed that vaccine therapy was responsible for amyloidosis in this case."

Dick and Leiter [12] produced amyloidosis in rabbits within eight months by the use of 17 bacterial strains which included hemolytic and green strains of streptococcus and Friedländer's bacillus. They found that the freshness of the bacterial strain seemed to be more important than the dosage in determining the rate and degree of amyloid production. Two observers [13, 14] noted that between 60 per cent and 80 per cent of horses used for the production of antisera developed amyloidosis. It was interesting to note that the horses employed for the production of scarlet fever antisera showed a greater incidence of amyloidosis than those used for diphtheria and tetanus antitoxin. Hardgrove [2] rapidly produced amyloid in mice by the injection of *Bacillus coli* and staphylococci and various proteins. However, bacterial vaccines and toxins are not the only substances which are known to cause amyloid disease. Letterer [15] produced it by repeated injections of casein, peptone, egg albumin, cereal albumin, gelatin, nuclein and implants of normal spleen and kidneys. Grayzel and his colleagues [16] maintain that in order to produce amyloidosis with these products the whole protein compound must be used, for if intermediary or split products are used, amyloidosis will not occur. In a Cabot Case Record report [17] the subject, a case of atrophic arthritis with amyloidosis, had received injections of amidoxyl benzoate during a period of nine months. Eklund and Reimann [18] also reported from the literature that the parenteral use of such substances as silicates, manganese chloride, sulfur, selenium, turpentine and others was followed by amyloidosis.

Two other patients from the dispensary received the Crowe's vaccine by injections for approximately the same length of time and as regularly as the case which is reported without evidence of amyloidosis.

Dr. H. Warren Crowe has personally used his vaccine extensively for many years at his clinic in London and the same vaccine has been employed in many clinics throughout the world. Also other types of vaccines which are widely used in other clinics in the treatment of atrophic arthritis include invariably several strains of streptococci. Thus it would appear that if parenteral injections of vaccines, particularly of streptococci, are possible agents for the production of amyloidosis, the complication would occur frequently; however, it has seldom

been reported in human cases. Furthermore, in tuberculosis, the disease with which amyloidosis is most frequently seen, parenteral therapy is seldom employed. It is, therefore, difficult to consider parenteral injections per se as the most important etiological factor for human amyloidosis.

Summary

A case of atrophic arthritis is reported with amyloidosis of the spleen, liver, kidneys and adrenals. Whether the amyloidosis in this case of arthritis was a complication of the disease, a result of the repeated injection of a vaccine containing strains of streptococci, or the combined effect of the two cannot be positively stated.

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CHRONIC COR PULMONALE WITH REPORT OF A CASE*

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LESIONS affecting the lesser circulation occur less frequently than those of the systemic. There is less chance of direct observation of these lesions, and the diagnosis of the conditions must be made by less direct methods than is the case where one is dealing with the commoner cardiovascular diseases.

It is customary to speak of right or left heart failure but such statements require a certain amount of mental reservation because of the closely integrated and interdependent functions of the lesser and greater circulations. Any degree of failure of either one immediately jeopardizes the anatomical and functional integrity of the other and reduces the chance of properly supplying oxygen to the organs and tissues of the body.

As Dry [1] has pointed out, any consideration of the diseases affecting the flow of blood through the pulmonary area must recognize that here, as in other organs, a great vascular reserve is provided, there being a "vascular area and a capillary bed far greater than ordinary functional demands can exceed."

The systolic blood pressure in the pulmonary artery of man is normally low, being about 20 mm. of mercury. The comparatively delicate structure of the pulmonary arterial tree and the thin wall of the right ventricle are anatomical evidence of this low normal pressure.

Obstruction to the flow of blood through the pulmonary circulation leads to increased pressure within this system. This rise in pressure, if maintained over a period of time, leads to sclerotic changes in the pulmonary arteries and arterioles and to hypertrophy of the right ventricle.

In this connection it has been shown by Haggart and Walker [2] that slightly more than half the pulmonary vascular bed can be obstructed without seriously affecting the circulation in general. If this amount is exceeded even slightly, circulatory failure is precipitated. Whether this holds true when the obstruction takes place slowly and progressively does not appear to have been answered. The experiments on which these figures are based made use of acute obstruction only.

Waring and Black [3] show, diagrammatically, the various points in the pulmonary circulation at which obstruction may take place, from congenital heart disease with arteriovenous shunt, on one hand, to mitral stenosis on the other and including pulmonary valve, pulmonary artery or its larger branches, pulmonary arterioles, the capillary bed, the veins and finally the mitral valve.

Obstruction at the mitral valve is doubtless the most common point but its location beyond the capillary bed produces little effect on oxygenation until circulatory failure supervenes; consequently the picture, when recognized, is impure and complicated.

Obstruction due to disease of the pulmonary veins is very uncommon. That due to obliteration of the capillary bed must be very extensive in order to produce "cor pulmonale" because here lies the greatest vascular reserve. Such conditions as diffuse carcinomatosis of the lungs, extensive pulmonary fibrosis, etc., are some of the causes which may produce typical symptoms by obstruction in this area. The question of emphysema per se as a cause of sufficient obstruc-

* Received for publication December 31, 1940.

tion in the capillary bed to produce increased blood pressure and right ventricular hypertrophy seems to be one on which opinion differs.

Probably conditions affecting the vascular bed of the lungs on the arterial and arteriolar side furnish the purest examples of overload and failure of the lesser circulation. Massive emboli occluding the main stem of the pulmonary artery or largely occluding both main branches are usually promptly fatal, through shock and anoxemia. These constitute a large percentage of the cases observed. Slower occlusion at this same point by a somewhat similar mechanism is uncommon. Barnes and Yater [4] report a case of failure due to an old thrombus in the main trunk and both branches of the pulmonary artery probably arising some three years before death, as emboli from an infected hand. Somewhat similar cases have been reported by Means and Mallory,[5] and by Jump and Baumann.[6] It is a case of this type which I wish to report.

Case Report

H. H. McV. was first observed in 1934, complaining chiefly of thrombophlebitis in the left leg. There had been thrombophlebitis in the right leg in 1931. The original attack was preceded by "influenza" and accompanied by chills and fever. The present attack was preceded for two or three days by pain in the abdomen and distention with gas. There had been three or four attacks of abdominal pain of similar character accompanied by palpitation since 1931. Questioning brought out the facts that he was troubled by a dry non-productive cough and by dyspnea on exertion.

The only other history of possible importance was of an operation for varicocele on the left, in 1917, and the fact that he smoked about 30 cigars a day while engaged largely in indoor work.

Physical examination revealed, in addition to the signs of old and recent thrombophlebitis: temperature, 99.4° F.; pulse, 104; blood pressure, 134 mm. Hg systolic and 68 mm. diastolic; atrophy of the left testicle; slight right varicocele and dilated veins on the surface of the scrotum. The lung fields were clear, and the heart was apparently normal save for tachycardia. The remainder of the examination was negative. No further investigation of the cardiovascular system was made at the time. The tachycardia, cough and dyspnea were blamed upon the acute process and the heavy smoking.

His urine was acid, the specific gravity was 1.032, and several red cells were seen per high power field in the centrifuged specimen. Several hyaline casts were seen. The hemoglobin was 16.4 grams per 100 c.c. and erythrocytes 4.08 millions. White and differential counts were not remarkable and the blood Wassermann reaction was negative.

Under the usual treatment the condition of the leg improved, the blood cells disappeared from the urine and, coincidentally, the dyspnea and cough were relieved.

Four years later the patient was seen again because for six months he had felt exhausted and weak and, on exercise, there were dyspnea, palpitation and weakness in the legs.

Physical examination revealed temperature, 98.4°; pulse, 90; blood pressure, 124 mm. Hg systolic and 80 mm. diastolic. He appeared somewhat pale. The arteries in the neck pulsated more than normally. There was no dependent edema, no swelling of the liver, and no râles at the lung bases. The percussion note over the lungs was booming and the breath sounds feeble suggesting emphysema. He was not cyanotic. He had always had prominent eyes and this feature seemed somewhat exaggerated. There was a tremor of the hands.

The urine was normal. The hemoglobin was 18 grams per 100 c.c.; red cells numbered 4.42 millions. Basal metabolic rate determinations were minus 19, plus

8 and minus 5 per cent over a period of two months, during which time he received small doses of thyroid extract.

The full significance of the symptoms was not appreciated at this time, but the patient was required to rest a great deal and soon he was symptomatically greatly improved. The symptom which never left him was dyspnea on exertion.

He returned in six months because, on resuming his usual activities, all the symptoms came back and were exaggerated. Exertion tended to bring on paroxysms of severe cough. These also occurred at night and, on at least two occasions, he lost consciousness momentarily during the coughing. Cyanosis now accompanied the dyspnea after exertion or on severe coughing.

At this time the pulse was 96 and blood pressure 120 mm. Hg systolic and 90 mm. diastolic. There was no dependent edema, no enlargement of the liver, nor râles in the lungs.

Fluoroscopic examination of the chest revealed a large heart with thickened vascular markings in the hila but no unusual pulsation was noted in the hilar vessels. Films at 72 inches (figure 1a) showed the heart to be enlarged to 52 per cent of the diameter of the chest. Enlargement was both to right and left and the shadow was of a globular shape. There was a marked bulge in the region of the pulmonary artery.

The electrocardiogram (figure 1b) showed a slight tachycardia and a marked right ventricular preponderance, with no other distinctive abnormalities.

The urine contained a strong trace of albumin and an occasional erythrocyte. The hemoglobin was 116 gm. per 100 c.c., and red cell count, 4.74 millions per cu. mm.

It was now recognized that we were dealing with a chronic cor pulmonale with signs of circulatory failure. These signs and symptoms were as follows: gradually increasing dyspnea out of all proportion to any other evidence of congestive heart failure. In particular, there had been no râles at the pulmonary bases. The dyspnea had been accompanied by an increasing degree of cyanosis on strain, such as cough or exertion. Accentuation of the pulmonary second sound, which is so often mentioned, was not a marked feature in this case. The roentgen examination revealed the typical right heart enlargement with prominence at the pulmonary cone. The electrocardiogram was characteristic with its evidence of marked right ventricular preponderance. That this picture was not due to mitral stenosis was obvious because of the absence of significant murmurs and of left auricular enlargement as proved by the roentgen observations.

Hospitalization with rest and digitalis caused marked improvement which lasted only until an attempt was made to permit physical activity. Then all the symptoms recurred and, in addition, there were dependent edema, enlargement of the liver, and finally, ascites. Râles were never heard in the lungs until the final week of life. Hemoptysis did not occur. Dyspnea remained the leading symptom. Cyanosis became more marked as a terminal feature but not to the extent suggestive of the so-called "black cardiac." He was, consequently, kept at rest much of the time.

Early in 1939 the patient was examined by Dr. T. J. Dry at the Mayo Clinic. An instructive additional finding was reported by him. This was an increase in circulation time from the normal 14 seconds to 35 seconds—arm to tongue, as determined by injection of 5 c.c. of decholin. It was assumed that the slowing was in the pulmonary circuit.

On two occasions, when compensation was at its best, a faint continuous murmur with systolic accentuation was heard over the pulmonic area.

The patient was comfortable at almost complete rest and with digitalis administration until July, 1939 when dyspnea increased, orthopnea became marked, cyanosis came on, and increased, and edema, liver enlargement and ascites became more and more marked. Venous pressure was markedly increased. On lying down the veins of the head and neck became tremendously distended and cyanosis and dyspnea became very marked.

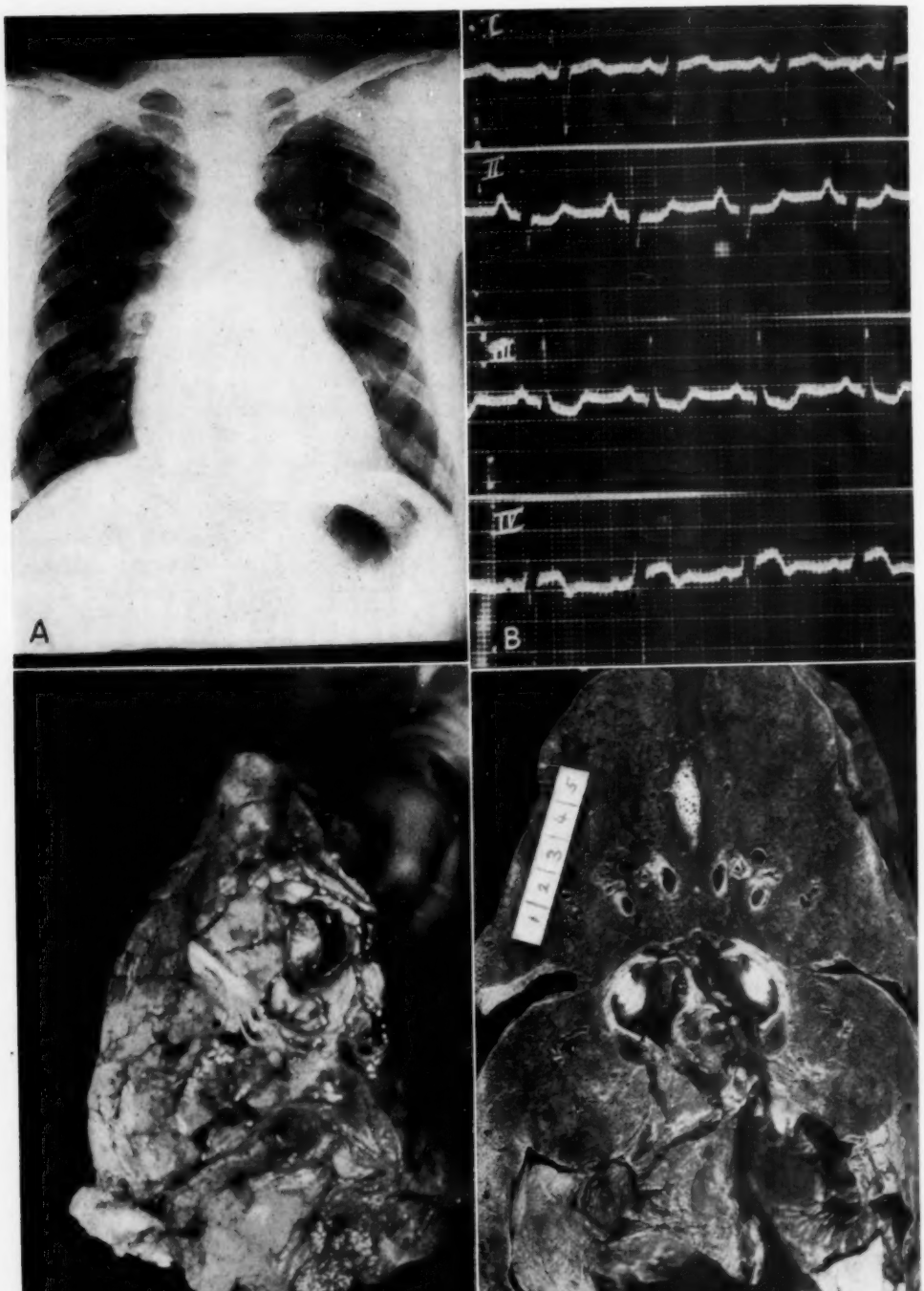

FIG. 1.

In the last few hours oxygen was given and no quantity up to 7 liters per minute made the slightest difference in his dyspnea and cyanosis. The heart became slower and the rhythm was broken by frequent ectopic beats. Gallop rhythm became so marked it seemed as if the ventricles were alternating in their contractions. A systolic murmur was audible over each valve area. The pulse was feeble and the blood pressure fell rapidly.

The clinical diagnosis at death on September 23, 1939 was chronic cor pulmonale due to some obstructive lesion in the lesser circulation, probably arteriolosclerosis.

At autopsy the important findings were confined to the heart and lungs. The heart was both dilated and hypertrophied, the weight being 560 grams. Its transverse diameter was 16 cm. The dilatation involved all chambers and was accompanied by relative insufficiency of mitral (10 cm.), tricuspid (15 cm.), and pulmonary (10 cm.) valves. The hypertrophy involved the right ventricle largely, its wall having a maximum thickness of 1 cm. The wall of the left ventricle was not thickened; the aortic valve and aorta throughout its length were normal.

The anterior surface of the heart was composed largely of right ventricle, the apex being very blunt and composed of right ventricle. The left ventricle could be seen at the obtuse margin. The right atrium was greatly dilated and its wall was somewhat fibrous in appearance. The pulmonary cone was greatly dilated. The coronary arteries were normal.

In each main pulmonary artery, beginning at about its middle, there was a large firm thrombus. This was securely attached in each instance to the anterior aspect of the artery wall (figure 1c). The maximum thickness of the thrombus was 1.5 cm. The lumina were so nearly filled by the thrombi that only a small crescent-shaped opening remained. This was filled with recent clot which may have been post mortem.

These old thrombi extended into the secondary branches of the artery, in some instances completely filling vessels of 1 cm. or more in size (figures 1d and 2a and 5b). The cut surfaces of the thrombi showed differences in color and consistency suggesting accretion over a period of time but did not appear to have become organized in any portion.

The right lung showed three dimpled scars in the pleura over the lower lobe. Beneath each of these was an area of fibrous tissue. There was also a recent infarct 2 cm. in diameter at the pleura. Near the lower margin of the left lung was a similar small recent infarct.

The large and medium sized branches of the pulmonary artery show a moderate streaking with atherosclerosis. The peripheral pulmonary tissue showed an obvious vesicular emphysema.

In addition to these findings, there were ascites, bilateral slight pleural effusion, moderate pericardial effusion, pleural and pleuropericardial adhesions on the right, chronic passive congestion of the liver and spleen and an old healed infarct of the right kidney.

Microscopic examination of the old thrombus showed that the portion near the intima had undergone organization whereas the more peripheral portions were largely fibrin in various stages of hyalinization. The outer layer of the artery wall, where the old thrombus was attached, showed extensive perivascular lymphoid cell infiltration.

The smaller arteries showed thickened medial coats with corresponding reduction of the lumina. Many were occluded by organized thrombi. In many instances canal-

FIG. 1. (a) Roentgenogram showing enlarged heart, prominent pulmonary cone and thickening of the hilar shadows. Note that the cardiac enlargement is marked toward the right and relatively less toward the left. (b) Electrocardiogram of this patient showing principally right ventricular preponderance. (c) Mesial surface of lung. Note the main pulmonary artery containing an old thrombus with a crescent-shaped postmortem clot outlining the patent portion of the lumen. (d) Section deeper in the lung showing more complete occlusion of the pulmonary artery by old thrombus.

ization of these thrombi had taken place (figure 2b). The arterioles, as a rule, showed no change.

There were areas of atelectasis and larger areas of emphysema. Many heart failure cells were scattered throughout the lung.

The sections of heart showed little beyond a marked hypertrophy of the individual fibers of the right ventricle which contrasted sharply with those of the left ventricle.

Examination of the remainder of the organs showed nothing but the expected changes.

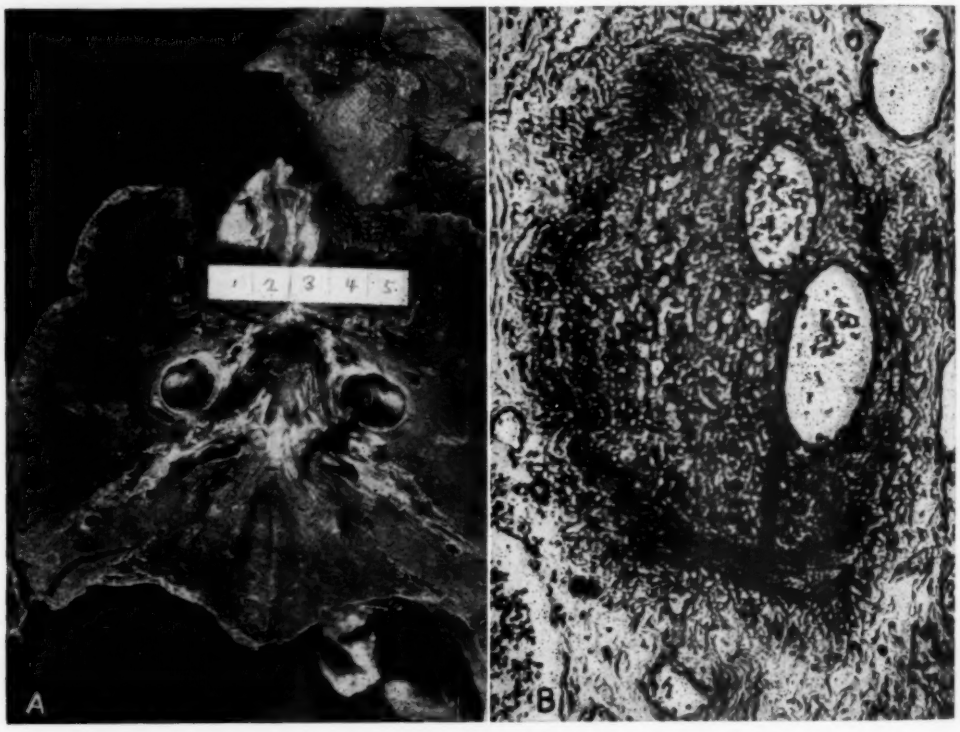

FIG. 2. (a) A section deeper into the lower lobe showing complete occlusion of branch of pulmonary artery 1.3 cm. in diameter. (b) Microscopic section showing small artery which has been completely thrombosed and recanalized.

DISCUSSION

The leading symptom in this individual was dyspnea. It was disproportional to the signs of congestive heart failure. There was but slight polycythemic response, and cyanosis occurred late. Right ventricular hypertrophy was obvious in the roentgenograms, and right ventricular strain was reflected by the electrocardiogram. There were no signs of pulmonary congestion until very late, when the left heart began to fail probably as a result of chronic anoxemia.

The life history of the lesion in the pulmonary arteries is not clear. Two episodes of thrombophlebitis, the first eight years before death and the second five years before death, suggest the possibility of embolism followed by gradual accretion of the thrombus, yet no definite history suggesting such embolic epi-

sodes could be obtained either from the patient or his wife. There is a possibility that the pulmonary artery participated in a primary vascular inflammatory process giving rise to mural thrombosis and that these thrombi grew by accretion until the clinical picture, as seen years later, gradually developed. There is some evidence to support the latter contention, inasmuch as the wall of the pulmonary artery showed some cellular infiltration suggestive of old inflammation and the clot was laminated, the oldest part lying next to the artery wall.

The amount of arteriolar sclerotic change was minimal and can be left out of consideration as a factor in producing anoxemia.

A certain amount of sclerotic change was present in the main stem and larger branches of the pulmonary artery but was inconsequential in amount when considered in relation to the symptoms. It was the effect, not the cause of increased intrapulmonary blood pressure.

Summary

1. The physiologic and pathologic consequences of obstruction in the pulmonary vascular bed are briefly reviewed.

2. A case of old bilateral thrombosis of both primary branches of the pulmonary artery is reported. This patient had the cardinal symptoms and signs of chronic cor pulmonale. This diagnosis was possible ante mortem, though the exact nature of the pathologic factor responsible for the clinical syndrome in this case could not be determined until autopsy.

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CALCIFICATION OF LEFT VENTRICULAR INFARCTION RECOGNIZED DURING LIFE *

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Calcified myocardial infarcts have been rarely found during life, and still more rarely proved at necropsy. Calcification in the heart was diagnosed during life by roentgen-ray in 1911 by F. M. Groedel.[1] The first case thus recognized and proved by necropsy was that of Thomas Scholz [2] in 1924. Cohen and

* Received for publication October 21, 1940.
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Levine [3] in 1937 reported the second case, which was also studied with the electrocardiograph. Parkinson [4] in 1938 added a third case proved at necropsy. Ours, the fourth case, was first discovered by roentgen-ray, and was studied with heart tracings and the kymograph. White [5] has stated that in rare cases actual bone is found in the myocardium instead of mere masses of lime salts. Necropsy in our case showed histological evidence of true bone formation. We have found seven other instances in the literature in which the calcium apparently has been absorbed and redeposited with the formation of true bone.

Case Report

A white male, 74 years old, entered the Sanitarium complaining of cough. There had been moderate dyspnea for one year. Three months previously he had a temperature of 103° F., with paroxysms of coughing productive of thick pyoid material. He was tired, could not get his strength back, had insomnia and nycturia. The remainder of his history was negative with the following exception. Nineteen years previously while caring for his furnace after breakfast he had had a momentary attack of sharp sticking substernal and epigastric pain, which took his breath away. After lunch, while selling bonds, he had a second similar but more severe attack which lasted an hour or two. Thirty-five minutes after his evening meal he had another attack. A physician was called at 10:30 p.m., made a diagnosis of angina pectoris, and gave him more than one hypodermic of morphine sulphate before leaving the bedside. He remained in bed 18 days, up about the house for 12 days, and then returned to light work schedule for eight months before resuming his regular work.

He was of sthenic habitus, 66″ tall, weighing 181 pounds. There were a few transient râles at both lung bases. The liver edge was not palpable. Blood pressure was 168 mm. Hg systolic and 100 mm. diastolic. Heart sounds were subnormal in

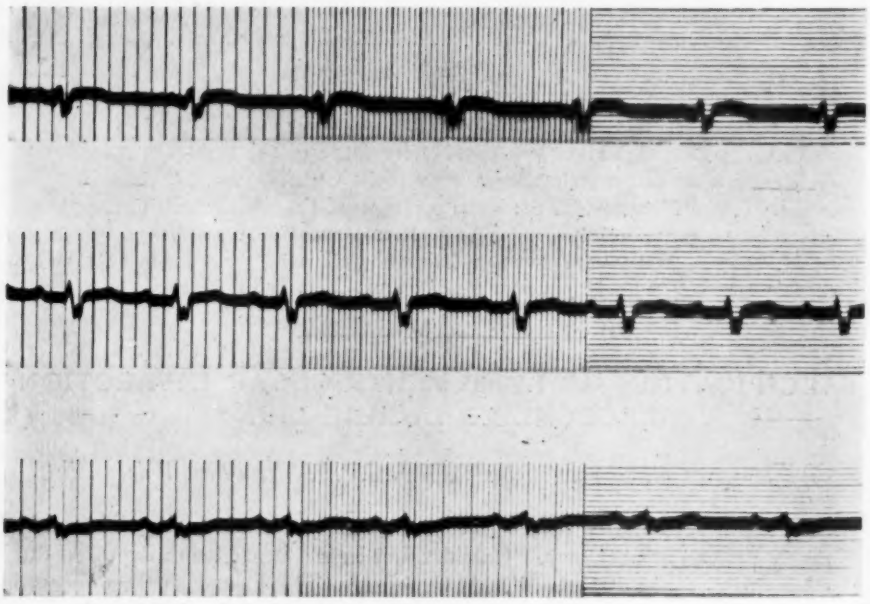

Fig. 1. Tracing 2 years before death showing low voltage, p-r 0.24 sec. Small Q_3, slurred R complexes (0.15 sec.). RT_1 elevated 1.3 mm. RT_2 elevated 0.5 mm. RT_3 depressed 0.3 mm. T_1 isoelectric, T_{1-3} slightly positive. T_1 or anterior type infarction, topographically, or the superficial sino-spiral muscle using Robb and Robb specific localization.

intensity, without murmurs, the apex not visible or palpable, and there was a gallop rhythm due to reduplication of the first sound.

Clinical impression: Organic heart disease (arteriosclerosis-hypertension; coronary disease; gallop rhythm; Class 2b).

Laboratory findings: Complete blood count negative. Urinalysis showed a trace of albumin and an occasional hyaline cast.

Electrocardiographic study showed low voltage, p–r 0.24 second. Small Q_1, slurred R_{1-2-3}, main deflections being negative in Leads I and II, and QRS 0.15 second duration. RT_1 elevated 1.3 mm., RT_2 elevated 0.5 mm. RT_3 depressed 0.3 mm. T_1 or anterior type infarction, topographically, or the superficial sino-spiral muscle involvement using Robb and Robb specific localization (figure 1).

Roentgenographic studies and fluoroscopic examinations showed vascular pulmonary engorgement. The heart was enlarged to the left, and the left portion of the

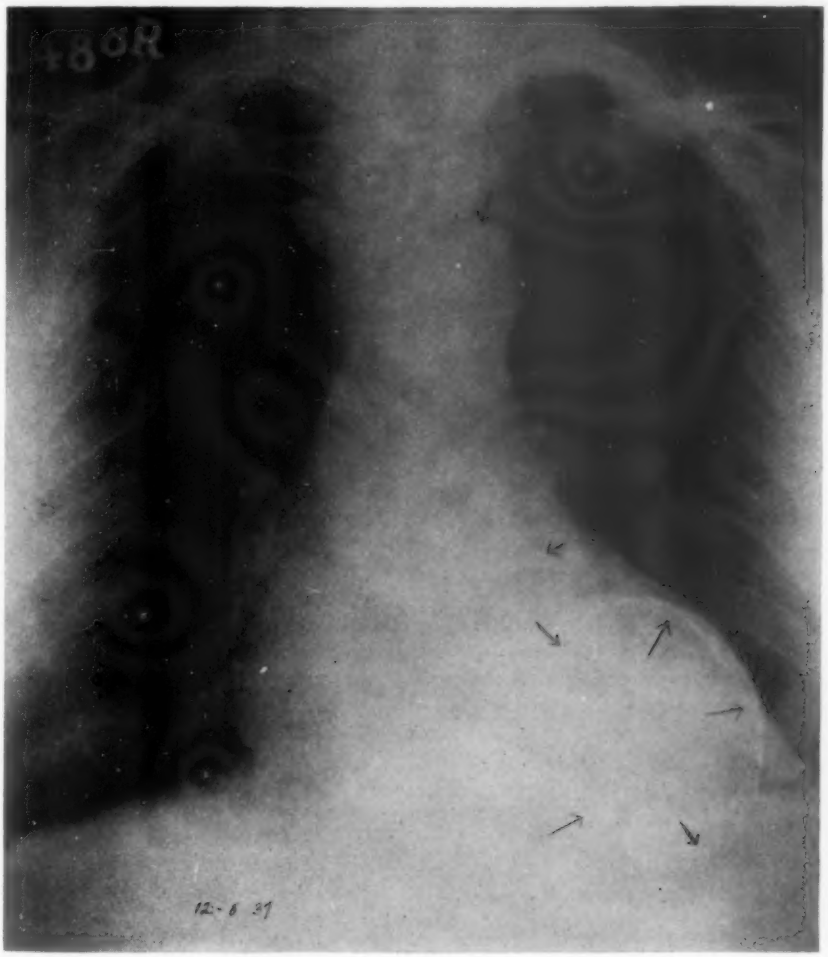

FIG. 2. Posteroanterior teleoroentgenogram. Heart moderately enlarged, especially to the left; large ovoid area of calcification, subpericardially located in apex and anterior wall of left ventricle, measuring 9 by 6 cm. Small arrow immediately above indicates areas of calcification in proximal branches of the left coronary artery. Arrows over aortic arch margin indicate definite arteriosclerotic changes of aorta.

heart, including the apex and lower third of the left border, was occupied by a dense ringlike shadow, which formed an oblong ring. The vertical diameter of this ring was 10.5 cm., transverse diameter was 8 cm. and 0.5 cm. in thickness. This was well visualized by Bucky radiographs in a–p, p–a, and right oblique positions. It was definitely established that the deposit of calcium extended to the edge of the lower left portion of the heart. In the lateral position the shadow had the appearance of a quarter-moon. Measurements: T. 32.0 cm., m.r. 6.0 cm., m.l. 12.5 cm., t.t. 18.5 (57.812 per cent). The aorta was elongated, the knob prominent to the left. It was believed from these findings that the ringlike shadow was probably calcium deposit in an old infarct following coronary occlusion, and was in the parietal wall of the left ventricle (figure 2).

FIG. 3. Posteroanterior kymogram. Almost complete absence of ventricle pulsations about midway between base and apex. (Large arrow.) Smaller arrow in lower frames shows almost complete absence of movement of calcified myocardium apex.

The patient rested six weeks in bed, began graduated exercises, and improved. His blood pressure fell to 126 mm. Hg systolic and 76 mm. diastolic. The gallop rhythm disappeared permanently on the ninth day, he lost 10 pounds, and returned home feeling much better.

About six months later kymograms showed a rather markedly diminished left ventricle contraction at the level of the nest-form calcification in the apex of the heart. The entire left ventricle was not involved in this diminished pulsation, the basal portion of the left border and the posterior border showing normal amplitude of excursion (figure 3).

Fourteen months later he returned with crepitant râles over the base of the left lung. Pulse rate was 96. Blood pressure was 150 mm. Hg systolic and 82 mm. diastolic. There was a tendency toward gallop rhythm, the tone quality of the heart sounds being poor. Heart tracings including Lead CF IV showed Q_1 more definite, and T_1 and T_2 slightly more positive. There was little if any depression in RT_3. Absence of P_4 and a large Q_4. RT_4 elevated (figure 4).

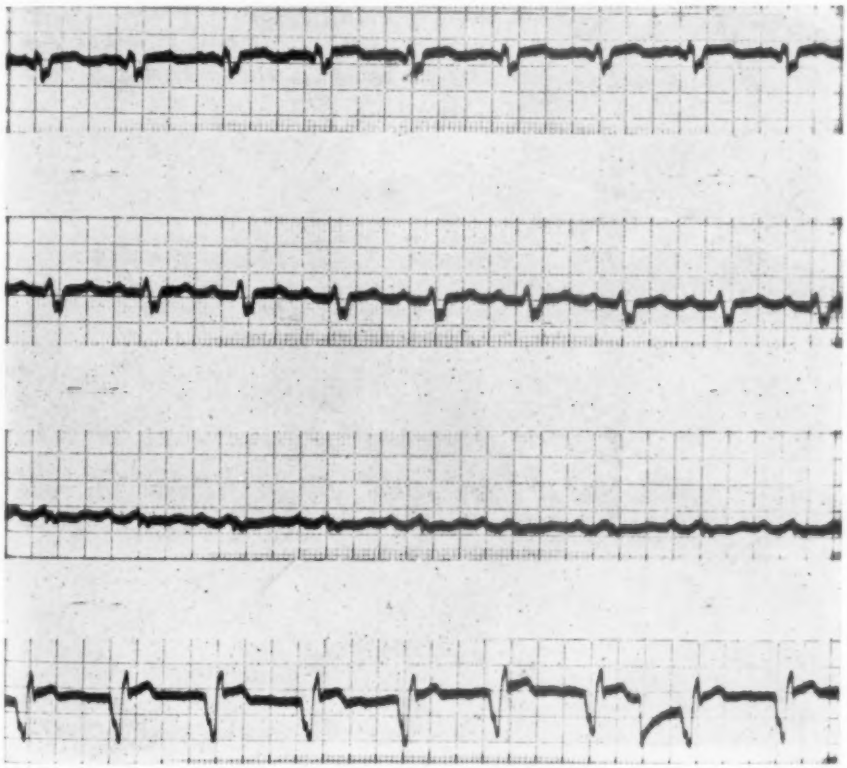

FIG. 4. Taken 9 weeks before death, includes Lead CF IV. T_1 and T_2 slightly more positive. Little if any depression in RT_3. Q_1 more definite. Lead IV shows absence of P wave and has a large Q_4. RT_4 elevated and T_4 falls at the highest point of RT_4; viz., at its termination.

Five weeks later he died in bed after climbing three flights of stairs to deliver a speech.

Postmortem examination: The only noteworthy finding was the condition of the heart. It measured 16 cm. from base to apex and 15 cm. transversely at the base.

It weighed 725 grams. The pericardium was almost universally adherent, with moderate extrapericardial fat. The anterior surface of the left ventricle had a firmly rounded, bulging appearance involving the lower half of the left ventricle and apex and was about 10 cm. in diameter, and separated from the upper portion of the left

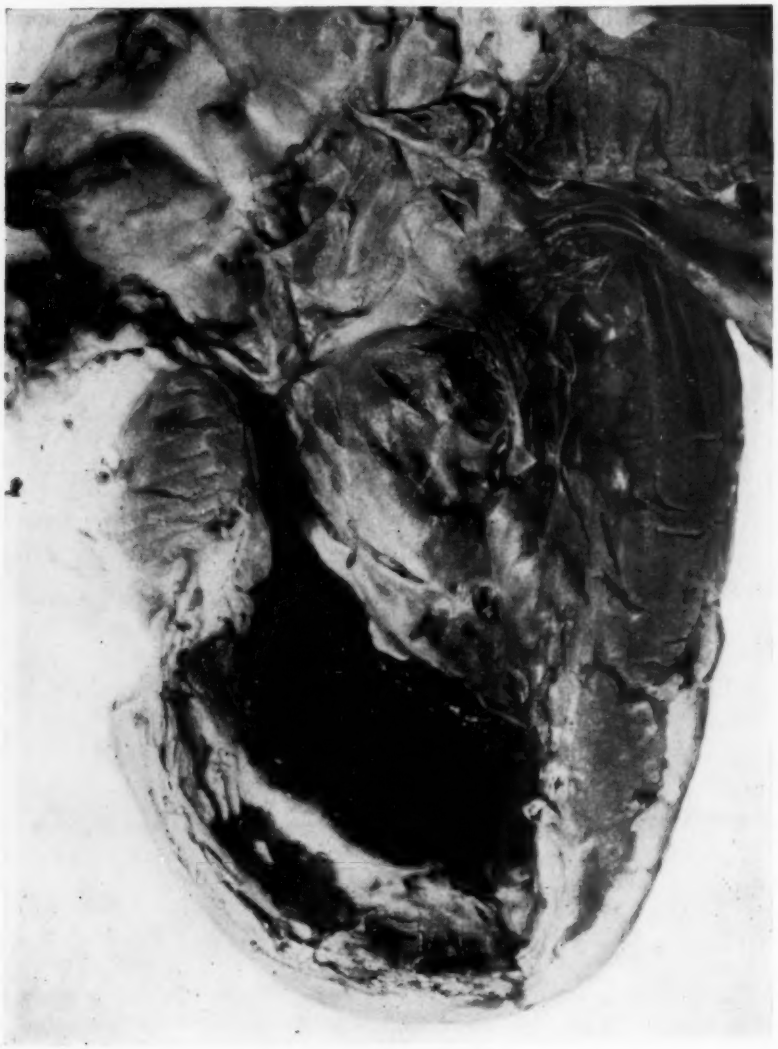

FIG. 5. Left ventricle exposed. The width of the heart muscle in the upper third of the left ventricular wall was 2.5 cm. Note the narrow wall and aneurysmal pouching of the lower two-thirds of the anterior left ventricular wall where the heart muscle has been replaced by scarring and calcification.

ventricle by a faintly visible and palpable groove. On palpation this bulging portion felt like bone and extended around the apex and along the posterior wall of the left ventricle for about 2 cm. Postmortem roentgenograms showed this calcification. When the left ventricle was opened (figure 5), it was seen that the area disclosed on the external aspect of the left ventricle corresponded to the wall of an aneurysmal

dilation, the wall of the aneurysm varying from 7 to 14 mm. in thickness. Its cut surface was gray-white and firm. Embedded in the wall between the layers of scar tissue and remnants of myocardium were plaques of calcification, some of which seemed to be ossified. The lining of the aneurysm was covered by a laminated, partially organized blood clot. At the apex there was a more recent partially organized polypoid mass of mural thrombus slightly more hemorrhagic and covered by fibrin. The aortic cusps were slightly sclerosed at the bases, and there were occasional streaks of fatty plaques on the intima of the aorta. The orifices of the coronary arteries were narrow. The main stems of both coronary arteries were greatly thickened and lined by atherosclerotic plaques, some of which were calcified. The anterior de-

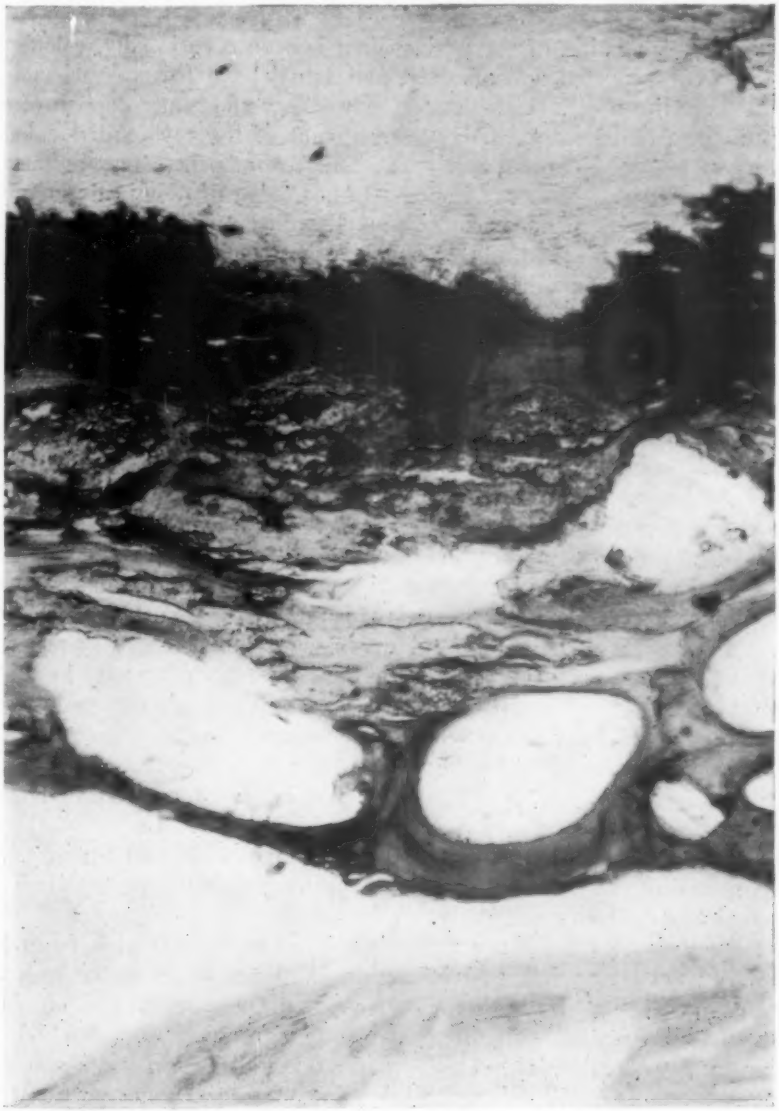

FIG. 6. Wall of aneurysm with calcification and trabeculae of bone.

scending branch of the left coronary was rigid and its lumen barely discernible. Other branches of the coronary arteries presented advanced calcification. Nowhere was there any gross evidence of recent thrombus formation.

Microscopic examination showed recanalization of old occlusions in the vessels, with intramural plaques of calcification frequently surrounded by remnants of scar tissue and myocardium in the wall of the aneurysm. In other areas definite bone formation could be demonstrated (figure 6).

The heart was preserved and presented to the Heart Museum of the University of Wisconsin Medical School, Madison, Wisconsin.

Discussion

Although calcification of the pericardium is seen occasionally, calcified heart muscle has been reported uncommonly, and actual bone formation has been reported in seven instances. Calcification may follow metastatic deposit of calcium or toxic myocardial damage. About 9 per cent of the myocardial calcification reported has followed coronary sclerosis and thrombosis. The increasing incidence of coronary disease, our improved knowledge of diagnostic criteria, and our increased facilities for more complete study of cases of coronary disease, will, no doubt, lead to increased finding of myocardial calcification.

Scholz [2] says that like other pathological calcifications in the heart, the calcium may be a deposit of calcium salts within the heart tissue, or it might occur as a precipitate, as is found in the endocardium. The deposition of calcium salts within the heart takes place only in dead, or markedly deteriorated, never in healthy tissue. The process begins with the deposit of fine calcium granules, usually calcium phosphate, within the broken up heart muscle fibers. These granules then gradually coalesce, forming plaques, and gradually involve all of the elements of the heart. The ultimate cause of the phenomenon seems to lie in the factors controlling the calcium tolerance of the cell and in the nature of the physiochemical processes within the individual cell.

It is interesting to consider the question as to why Nature has formed true bone in this calcified tissue in the heart. It is possible that such bone would serve the heart more effectively than amorphous or crystalline calcium in preventing a rupture of the weakened heart muscle for the bone trabeculae may be laid down with reference to stress and lines of force. Further, we may ask as to the origin of the osteoclasts and osteoblasts which has never been definitely settled. The occurrence of these cells would suggest the possible correctness of the belief of Wingate Todd that the osteoblasts are fibroblasts or connective tissue cells which have undergone certain characteristic modifications. Certainly, the change from calcium deposit to true bone formation suggests that an attempt is being made to specialize the cells and produce a working tissue, a process seen in life phylogenetically and ontogenetically.

The diagnosis of cardiac aneurysm is seldom made, although from Parkinson's study [4] aneurysm followed infarction in 9 per cent of the cases. Our case would have escaped attention if roentgenographic study had not been requested. In all cases of heart disease, roentgenographic study should be made. In order to detect conditions which would otherwise escape the attention of pathologists, Scholz roentgen-rays all specimens routinely at postmortem examination.

It is also of interest [1] that our patient lived 21 years after his infarction, 19 of those 21 years without the knowledge of or symptoms of heart disease. Furthermore, his recovery followed only 18 days of rest in bed. Although it probably takes six or eight weeks for fibrous replacement of infarcted heart tissue, 18 days of rest were sufficient in this instance, suggesting how great are the recuperative powers of the heart.

The author wishes to thank F. W. Mackoy, W. F. Ragan, J. E. Habbe, and Norbert Enzer, physicians, for their help in the study of this patient, and Mr. Leo C. Massopust, Marquette University, who prepared all the illustrations.

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5. White, Paul D.: Heart disease, 1931, The Macmillan Company, New York.

EDITORIAL

EPIDEMIC KERATOCONJUNCTIVITIS

This disease, which first appeared in epidemic form in the United States in California and Oregon in 1941, has become so widely distributed in this country that it constitutes a serious menace by reason of the disability it causes among workmen as well as the visual impairment suffered by some of its victims. The present outbreak was preceded by an epidemic in Hawaii in 1940, from which it was presumably brought to San Francisco where it caused an extensive epidemic among shipyard workers. Good clinical descriptions of the disease have been published by Hogan and Crawford [1] in San Francisco, by Rieke [2] in Oregon, and by Sanders et al.[3] in a smaller group of cases in New York.

The disease is conveyed from one person to another by direct contact, but it appears as a rule not to be highly contagious. Transmission to other members of a family occurs occasionally but is not the rule. Working in close contact under unhygienic conditions seems to favor its spread. Minor injuries to the eye and other types of inflammation are thought by some to be important predisposing factors.

After an incubation period of about five to 12 days, the patient complains of burning in one eye, often of a foreign body in the eye. The eye shows signs of an acute conjunctivitis, first limited to the lids, especially the lower lid. There is intense congestion, chemosis and edema which later extend to the bulbar conjunctiva. In severe cases a pseudomembrane may form, removal of which leaves small bleeding spots. A striking feature is the scantiness of the exudate which is mucoid or watery, never purulent, and contains lymphocytes. Smears and cultures from the exudate are sterile or show no organisms of significance, and no inclusion bodies.

The conjunctivitis may be preceded by mild systemic symptoms, headache, pain over the infected eye, slight fever and malaise, regularly so in severe cases. In a large majority of the cases the preauricular lymph nodes are enlarged and tender, occasionally also the submentals and upper cervicals.

In about half the cases the second eye becomes involved after a few days, but the inflammation is usually less intense. Simultaneous involvement of both eyes is rare.

After about one to two weeks (2 to 38 days) keratitis appears in from 50 to 85 per cent of the cases, often accompanied by pain, photophobia and lacrimation. Slight degrees of involvement may be missed unless repeated

[1] Hogan, M. J., and Crawford, J. W.: Epidemic keratoconjunctivitis. (Superficial puntate keratitis, keratitis subepithelialis, keratitis maculosa, keratitis nummularis), Am. Jr. Ophth., 1942, xxv, 1059–1078.

[2] Rieke, F. E.: Epidemic conjunctivitis of presumed virus causation, Jr. Am. Med. Assoc., 1942, cxix, 942–943.

[3] Sanders, M., Gulliver, F. D., Forchheimer, L. L., and Alexander, R. C.: Epidemic keratoconjunctivitis, Jr. Am. Med. Assoc., 1943, cxxi, 250–255.

examinations are made with a slit lamp. The keratitis may be limited to one eye, or as in 28 of Sanders' 42 cases with keratitis, the second eye may become involved a few days after the first. The keratitis manifests itself by the appearance of small grayish discrete spots about 0.5 mm. in diameter, which may coalesce to form larger areas. The spots may be sparse or very numerous, are chiefly in the exposed portions of the cornea, and are more numerous in the central pupillary area than in the periphery. They are located in the superficial portion of the substantia propria beneath Bowman's membrane. Herpetiform vesicles or superficial ulcerations which stain with fluorescein are very rare, and corneal sensation is usually retained. Vascularization never occurs. Once formed, these infiltrates are often very persistent. The keratitis may continue in an acute form and disability may persist for as long as eight weeks. In Sanders' series, in 71 per cent of the cases there was disability lasting from one to eight weeks.

In some of the reported cases the infiltrates gradually disappeared after from one week to several months, but in many cases they persisted for from six months to two years, and in some presumably they will be permanent.

The degree of visual impairment has varied in different epidemics. Sanders reported that in one-third of the cases with keratitis there was a loss of vision of from 5 to 15 per cent. Others have reported greater impairment, from 20/55 to 20/66. Hogan and Crawford reported that in most cases with visual impairment, 20/30 vision was regained within about three months. Such a degree of visual loss, however, may last many months and probably will be permanent in some cases. Many patients complain of halos, especially about bright artificial lights. Complete loss of useful vision, however, rarely if ever occurred, and scars have formed only in rare cases in which there had been superficial abrasions of the cornea.

Until recently the cause of the disease was unknown. There has been general agreement that it is not a bacterial infection. Sanders and his associates,[4, 5] however, have obtained strong evidence that the agent is a filterable virus. By inoculation of material from the eye of two human cases intracerebrally into white mice, they succeeded in producing an infection which could be propagated only through a short series of mice. However, if ground up brain tissue from an infected mouse was inoculated into a tissue culture medium composed of embryonic mouse brain and serum ultrafiltrate, multiplication of the virus occurred, and there was an enhanced virulence for mice, so that infection by intracerebral inoculation was uniformly fatal and the virus could be maintained indefinitely. Young unweaned mice could be infected also by intraperitoneal injection. Rabbits also could be infected by intracerebral inoculation, but rats and guinea pigs were resistant. One human volunteer was infected by inoculation into the conjunctiva, and infection was apparently produced in a similar manner in two monkeys. The

[4] SANDERS, M.: Epidemic keratoconjunctivitis ("Shipyard conjunctivitis"). I. Isolation of a virus, Arch. Ophth., 1942, xxviii, 581–586.

[5] SANDERS, M., and ALEXANDER, R. C.: Epidemic keratoconjunctivitis. I. Isolation and identification of a filterable virus, Jr. Exper. Med., 1943, lxxvii, 71–96.

virus passed readily through Berkefeld and Seitz filters, and through collodion membranes with a pore diameter of 75 millimicra.

By intraperitoneal injection of serum-virus mixtures into unweaned mice, Sanders was able to demonstrate protective substances in the serum of convalescent patients. In seven cases, including the experimentally infected volunteer, they demonstrated protective substances in individuals whose serum had been inactive in the acute stage of the disease. By suitable crossed protection tests they demonstrated the identity of the two strains of virus isolated. The serum of convalescent patients in California protected mice from the virus strains isolated from cases in New York. They also demonstrated that this virus was immunologically distinct from that of lymphocytic choriomeningitis, of Theiler's spontaneous mouse encephalomyelitis, and of ordinary herpes. It seems highly probable, therefore, that this virus is the specific causative agent of the disease.

Although this disease is new to most physicians in this country, many reports of similar epidemics have been published. Although it is impossible now to prove that the etiological agent in these epidemics was immunologically identical with Sanders' virus, the clinical descriptions are essentially identical with those of the present epidemic. One of the best early descriptions is that of Fuchs,[6] who reported 36 cases. He described the initial conjunctivitis with catarrhal nonpurulent exudate; the late appearance of the keratitis, as the conjunctivitis was subsiding; the development of 'punctate' opacities 0.5 mm. or more in diameter beneath Bowman's membrane, without superficial ulcerations; and the protracted course with frequent persistence of the opacities for six months to a year. Many descriptions of similar epidemics appeared in the German literature from 1938 to 1941.[7]

Among others reporting similar epidemics may be mentioned: Herbert, 226 cases from Bombay in 1901; Wright, 3500 cases from Madras in 1930; Doggert, 44 cases from London in 1933; Ling, an epidemic in China in 1936; Houwer, in Java in 1938; Hamilton, in Tasmania in 1941; and Viswalingen, 3500 cases in Malaya in 1941. Hobson in 1938 reported 16 cases in a veterans' hospital in San Francisco. The disease, therefore, is not altogether new in the United States.

The disease is self-limited, but no form of treatment has been shown to influence its course. Strong antiseptic solutions are injurious. Sulfathiazole locally has not been definitely helpful. Braley and Sanders[8] in a small uncontrolled series of cases reported promising results from the intravenous administration of 20 to 50 c.c. of convalescent serum. This procedure merits further trial, but the evidence supporting it is still very meager.

[6] FUCHS, E.: Keratitis punctata superficialis, Wien. klin. Wchnschr., 1889, ii, 837–841.
[7] SMETMANS, F. K., et al.: Aussprache über die Keratokonjunctivitis epidemica, Med. Klin., 1939, xxxv, 235–237.
[8] BRALEY, A. E., and SANDERS, M.: Treatment of epidemic keratoconjunctivitis, Jr. Am. Med. Assoc., 1943, cxxi, 999–1000.

Although there is some dispute as to the degree of contagiousness of the disease, there is no doubt that it is conveyed by direct contact. The only practicable means now available to limit spread of the infection is isolation of the patient at the onset of the infection. Since it is difficult or impossible to make a definite diagnosis at this time, it will be necessary to exclude from work every individual with an inflamed eye until a positive diagnosis can be made or until the inflammation has subsided. Although such measures seem drastic, they appear indispensable if serious interruptions of work schedules are to be avoided. Meticulous asepsis on the part of examining physicians is equally imperative.

REVIEWS

Anoxia, Its Effect on the Body. By EDWARD J. VAN LIERE, Ph.D., M.D. 269 pages; 23 × 15.5 cm. The University of Chicago Press, Chicago, Illinois. 1942. Price, $3.00.

This is a carefully composed analytical monograph on the subject of anoxia, written by an eminent investigator, and represents an epitome of the important contributions to our knowledge of this subject.

It evidences a complete and meticulous search of the existing literature, is completely authenticated, and, through the author's suggestions often found at the end of each section, should provide investigators in these problems a rich source of suggestions for further research.

Little detailed or technical data are given and illustrations are few, but the material has been so edited that essential facts are not distorted. The excellent footnotes and index render this work applicable as a source-book. The clarity and straightforward manner in which the information is presented provides the internist or flight surgeon with a valuable source of basic knowledge.

J. A. W.

Gynecologic Surgery. By MORRIS A. GOLDBERGER, M.D., F.A.C.S. 164 pages; 22 × 14 cm. Oxford University Press, New York City. 1942. Price, $2.00.

As Dr. Goldberger states in the preface, "this cannot replace the full standard text books of Gynecology," but there is definitely a place for this outline in the library of every student and specialist. The outline is logical in its approach, and reflects the author's keen mind and ability. The procedures recommended have all been carefully selected and have stood the test of time.

The brief outline of the anatomy and pathology should be helpful to both students and practitioners. The blank pages are a feature which should be incorporated in more books.

In general it is an excellent book.

W. K. D.

BOOKS RECEIVED

Books received during March are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Brucellosis in Man and Animals. Revised Edition. By I. FOREST HUDDLESON, D.V.M., M.S., Ph.D. Contributing authors: A. V. HARDY, M.S., M.D., Dr.P.H., J. E. DEBONO, M.D., M.R.C.P., and WARD GILTNER, D.V.M., M.S., Dr.P.H. 379 pages; 23 × 16 cm. 1943. Commonwealth Fund, New York, N. Y. Price, $3.50.

Doctor in the Making. By A. W. HAM, M.B., and M. D. SALTER, M.A., Ph.D. 179 pages; 20 × 13.5 cm. 1943. J. B. Lippincott Co., Philadelphia. Price, $2.00.

Behind the Sulfa Drugs. By IAGO GALDSTON, M.D. 174 pages; 19.5 × 13 cm. 1943. D. Appleton-Century Co., New York, N. Y. Price, $2.00.

Vascular Spasm—Experimental Studies. By ALEXANDER JOHN NEDZEL, M.D., M.S. 151 pages; 27.5 × 19.5 cm. 1943. University of Illinois Press, Urbana, Illinois. Price, $2.75 (clothbound); $2.25 (paperbound).

Chemotherapy of Gonococcic Infections. By RUSSELL D. HERROLD, B.S., M.D. 137 pages; 25 × 17 cm. 1943. C. V. Mosby Co., St. Louis, Missouri. Price, $3.00.

Contribucion al estudio anatomo clinico de las afecciones del endocardio. Tesis de doctorado por el Dr. MANUEL PEREA MUÑOZ. 363 pages; 27 × 18.5 cm. 1942. Universidad Nacional de Buenos Aires—Facultad de Ciencias Medicas.

Tables of Food Values. Revised and Enlarged Edition. By ALIVE V. BRADLEY, M.D. 224 pages; 25.5 × 20 cm. 1943. Manual Arts Press, Peoria, Illinois. Price, $3.50.

COLLEGE NEWS NOTES

Additional A. C. P. Members in the Armed Forces

Already published in preceding issues of this journal were the names of 1,364 Fellows and Associates of the College on active military duty. Herewith are reported the names of 48 additional members, bringing the grand total to 1,412.

Glen I. Allen

Walter F. Berberich
William L. Bettison
Philip B. Bleecker
J. Russell Brink
Frederick S. Bruckman

George B. Craddock

Herbert D. Edger
Frederick A. Eigenbrod
George F. Ellinger

Marcel J. Foret
Julian M. Freston

John E. Garcia
Charles C. Gill
Bernard A. Goldman
Abraham M. Gordon
Edwin M. Goyette

Russell B. Hanford
Thomas J. Hanlon
J. Watson Harmeier
Ferdinand C. Helwig
Kelse M. Hoffman
Joseph L. Hollander
Willard F. Hollenbeck

Charles A. Jones
Murrel H. Kaplan

Andrew J. Klein
Rudolph A. Kocher
Milton L. Kramer
Isadore J. Kwitny

Alan N. Leslie

Roscoe F. Millet

Marshall G. Nims

Alexander P. Ormond

George M. Powell

Charles J. Roberts

Robert B. Skinner
Hyman A. Slesinger
William Stein
Joseph B. Stevens
Paul S. Strong
Paul R. Swanson

Charles M. Thompson

Arie C. van Ravenswaay
Stoughton R. Vogel

Clarence B. Whims
Major S. White
Willard H. Willis

New Life Members of the College

The following Fellows of the American College of Physicians have subscribed to Life Membership, and their initiation fees and Life Membership subscriptions have been added to the permanent Endowment Fund of the College:

Dr. V. Thomas Austin, Urbana, Ill.
Dr. Seymour Fiske, New York, N. Y.
Dr. Herbert T. Kelly, Philadelphia, Pa.
Dr. John T. Murphy, Toledo, Ohio
Dr. Harold Orr, Edmonton, Alta.

Gifts to the College Library

We gratefully acknowledge receipt of the following gifts to the College Library of Publications by Members:

Books

Dr. Ernest E. Irons, F.A.C.P., Chicago, Ill.—"The Last Illness of Sir Joshua Reynolds" and "Theophile Bonet, 1620–1689,—His Influence on the Science and Practice of Medicine";
Dr. Peter J. Steincrohn, F.A.C.P., Hartford, Conn.—"Heart Disease Is Curable."

Reprints

Dr. Daniel M. Brumfiel, F.A.C.P., Saranac Lake, N. Y.—7 reprints;
Dr. Richard M. Burke, F.A.C.P., Oklahoma City, Okla.—1 reprint;
Abraham G. Cohen (Associate), Major, (MC), U. S. Army—1 reprint;
Joseph H. Delaney (Associate), Captain, (MC), U. S. Army—1 reprint;
Charles A. Flood, F.A.C.P., Major, (MC), U. S. Army—3 reprints;
Dr. Murray B. Gordon, F.A.C.P., Brooklyn, N. Y.—13 reprints;
Dr. Andrew C. Ivy, F.A.C.P., Chicago, Ill.—1 reprint;
R. Harold Jones, F.A.C.P., Major, (MC), U. S. Army—2 reprints;
Dr. William G. Leaman, Jr., F.A.C.P., Philadelphia, Pa.—3 reprints;
Dr. Francis M. Pottenger, Jr., F.A.C.P., Monrovia, Calif.—1 reprint;
Dr. Richard Kohn Richards (Associate), North Chicago, Ill.—10 reprints;
Dr. Michael W. Shutkin (Associate), Milwaukee, Wis.—2 reprints;
Dr. William C. Voorsanger, F.A.C.P., San Francisco, Calif.—1 reprint.

Dr. Israel M. Rabinowitch, F.A.C.P., Montreal, Que., has donated to the College Library of Publications by Members a set of seven manuals on Chemical Warfare, which he prepared for the Office of the Director of Civil Air Raid Precautions.

Schedule of Examinations by Certifying Boards

American Board of Internal Medicine:
William A. Werrell, M.D., Assistant Secretary
1301 University Ave.
Madison, Wis.

Written Examinations: Will be given in various cities and a number of Army and Naval stations, October 18, 1943. Applications must be filed before September 1.

Oral Examinations: Philadelphia, Pa., May 26–29, 1943; Chicago, Ill., June 9–11, 1943; New Orleans, La., and San Francisco, Calif., dates to be announced later. Oral examinations for certification in the sub-specialties, Allergy, Cardiovascular Disease, Gastroenterology, and Tuberculosis, will be held in conjunction with the oral examinations in internal medicine.

American Board of Dermatology and Syphilology:
C. Guy Lane, M.D., Secretary
416 Marlboro St.
Boston, Mass.

Written Examinations: Will be given in various cities, September 27, 1943.

Oral Examinations: Philadelphia, Pa. November 5–6, 1943.

AMERICAN BOARD OF PATHOLOGY: F. W. Hartman, M.D., Secretary Henry Ford Hospital Detroit, Mich.	*Written and Oral Examinations:* Chicago, Ill., June 2–3, 1943.
AMERICAN BOARD OF PEDIATRICS: C. A. Aldrich, M.D., Secretary 707 Fullerton Ave. Chicago, Ill.	*Written Examinations:* Will be given in various cities, October 8, 1943. *Oral Examinations:* New York, N. Y., November 20 or 21, 1943.
AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY: Walter Freeman, M.D., Secretary 1028 Connecticut Ave., N.W. Washington, D. C.	*Written Examinations:* Dates and place will be announced later. *Oral Examinations:* New York, N. Y., probably December 20–21, 1943.
AMERICAN BOARD OF RADIOLOGY: B. R. Kirklin, M.D., Secretary Mayo Clinic Rochester, Minn.	*Oral Examinations:* Chicago, Ill., June 3–5, 1943.

For further information and application forms communicate with the respective secretaries.

A. C. P. REGIONAL MEETING FOR MONTANA AND WYOMING

A Regional Meeting of the American College of Physicians for the States of Montana and Wyoming was held in Great Falls, Montana, May 1, 1943, under the direction of Dr. Ernest D. Hitchcock, F.A.C.P., College Governor for Montana. The scientific program of the meeting was as follows:

MORNING SESSION

Presiding Officer

DR. GEORGE E. BAKER, F.A.C.P.
Casper, Wyo.

"Water Balance in Consideration of Edematous Patients"—Dr. F. R. Schemm, F.A.C.P., Great Falls, Mont.

"Factors in Prognosis in Coronary Disease, Old Hearts Under the Strain of War"—Dr. Harold W. Gregg, F.A.C.P., Butte, Mont.

"Glycosuria, Blood Sugar Curves"—Dr. A. R. Foss, F.A.C.P., Missoula, Mont.

"Chemo-Prophylaxis"—Dr. Thomas F. Walker, F.A.C.P., Great Falls, Mont.

AFTERNOON SESSION

Presiding Officer

DR. ERNEST D. HITCHCOCK, F.A.C.P.
Great Falls, Mont.

"Rocky Mountain Spotted Fever"—Dr. George E. Baker, F.A.C.P., Casper, Wyo.

"Air Evacuation of Battle Casualties"—Scott M. Smith (by invitation), Lieutenant Colonel, (MC), U. S. Army.

"Yellow Fever Prophylaxis"—Dr. M. V. Hargett, F.A.C.P., U. S. Public Health Service, Hamilton, Mont.

"The Use of the Blood Groups in the Tracing of Racial Origins and Migrations"—P. B. Candela (by invitation), Lieutenant, (MC), U. S. Army.

"Allergy in General with Special Reference to Newer Developments"—Dr. M. A. Shillington, F.A.C.P., Glendive, Mont.

"Management of the Menopause with Special Reference to the Newer Synthetic Estrogens"—Dr. Earl L. Hall (by invitation), Great Falls, Mont.

This meeting concluded with a dinner meeting in the evening at which Dr. William G. Richards, F.A.C.P., Billings, Mont., spoke on "Hyperthyroid and the Neurotic as Illustrated by Shakespeare's Characters of Macbeth and Hamlet" and John L. Slattery, Attorney-at-Law, Great Falls, Mont., on "Some Observations."

Under the auspices of the Carlos Finlay Institute of the Americas and with the cooperation of the American Medical Association, the American College of Physicians, the American College of Surgeons, the American Drug Manufacturers Association, the American Hospital Association, the American Pharmaceutical Manufacturers Association, the American Pharmaceutical Association, the American Surgical Trade Association, the Wholesale Surgical Trade Association, and the National Physicians Committee, the National Conference on Planning for War and Post War Medical Services was held in New York, N. Y., Monday, March 15, 1943. Dr. James E. Paullin, F.A.C.P., President of the College, Atlanta, Georgia, presided at the morning session and Fred Rankin, Brigadier General, (MC), U. S. Army, President of the American Medical Association, presided at the afternoon session. Among the Fellows of the College who participated in the program were:

Thomas T. Mackie, F.A.C.P., Lieutenant Colonel, (MC), U. S. Army—"War and the Migration of Tropical Diseases";

Dr. John B. Youmans, F.A.C.P., Nashville, Tenn.—"Nutritional Diseases as a Post War Problem."

On September 29, 1942, the War Department acquired the Greenbrier Hotel at White Sulphur Springs, W. Va., and has designated it as the Ashford General Hospital in honor of the late Bailey K. Ashford, F.A.C.P., Colonel, (MC), U. S. Army.

Colonel Ashford was born in Washington, D. C., in 1873, and entered the Medical Corps of the U. S. Army in 1897. In 1910 he was a delegate to the International Congress of Industrial Hygiene and Alimentary Hygiene in Brussels. In 1917 he sailed with the First Division for France and later became Chief Surgeon of the Sixth Army Corps. After the war he was transferred to the General Staff in Washington and was made Editor-in-Chief of the Official Medical History of the War. Colonel Ashford was awarded many signal honors. A few of these were the Distinguished Service Medal, the Order of St. Michael and St. George of England, the Order of the Nile of Egypt, and degrees of Doctor of Science from the Universities of Georgetown, Columbia, Egypt and Puerto Rico. Colonel Ashford became a Fellow of the American College of Physicians on March 10, 1923, and served as College Governor of Puerto Rico for many years.

On March 21, 1943, James S. Simmons, F.A.C.P., Brigadier General, (MC), U. S. Army, delivered the commencement address at the special graduation exercises for the Washington University Schools of Medicine, Dentistry and Nursing at St. Louis, Mo. General Simmons spoke on "New Horizons in Military Medicine."

Dr. Jacob C. Geiger, F.A.C.P., San Francisco, Calif., was recently given the award of Fellow and "Member Correspondiente" of the National Academy of History of Panama.

The honor was granted upon recommendation of the Head of the Department of Education of Panama and approved by the President of the Academy at its session, February 15, 1943. The award was accompanied by a diploma, an honorary doctorate degree and citation, "For your relevant personal and scientific merits and for work in public health and service to Panama."

At a recent meeting of the Medical Board of the Philadelphia General Hospital, Philadelphia, Pa., Dr. Russell S. Boles, F.A.C.P., was elected President, Dr. Samuel B. Hadden, F.A.C.P., Secretary, and Dr. Lauren H. Smith, F.A.C.P., Treasurer.

Harold J. Harris, F.A.C.P., Lieutenant Commander, (MC), U. S. Naval Reserve, spoke on "Brucellosis: Its Diagnosis, Differential Diagnosis and Treatment" at one of the Friday Afternoon Lectures of the New York Academy of Medicine, March 19, 1943.

Dr. Louis L. Perkel, F.A.C.P., Jersey City, N. J., Dr. Sigurd W. Johnsen, F.A.C.P., Passaic, N. J., and Dr. Hyman I. Goldstein (Associate), Camden, N. J., participated in the scientific program and discussions at the March meeting of the New Jersey Gastro-enterological Society held in Glen Ridge.

Ellis H. Hudson, F.A.C.P., Lieutenant Commander, (MC), U. S. Naval Reserve, recently delivered a series of four lectures at the Mayo Clinic, Rochester, Minn., on malaria and other tropical diseases.

Dr. Richard Kohn Richards (Associate), North Chicago, Ill., addressed a meeting of the Society for Experimental Biology and Medicine in Chicago on March 9, 1943. Dr. Richards spoke on "The Rôle of Liver and Kidney in the Action of Dicumarol."

Under the Presidency of Dr. Joseph D. McCarthy, F.A.C.P., Omaha, Nebr., the National Conference on Medical Service held its 17th Annual Meeting in Chicago, Ill., February 14, 1943.

Dr. David J. Davis, F.A.C.P., will retire September 1, 1943, as Professor and Head of the Department of Pathology, Bacteriology and Public Health and as Dean of the University of Illinois College of Medicine, Chicago. Dr. Davis has been associated with the Medical School for twenty-nine years and was named Professor of Pathology in 1914 and Dean in 1925.

The 92nd Annual Session of the Iowa State Medical Society was held in Des Moines April 29–30, 1943. Among those who participated in the program were:

Dr. Harry L. Smith, F.A.C.P., Rochester, Minn.—"Coronary Disease: Its Recognition and Management";

Dr. James A. Greene, F.A.C.P., Iowa City, Iowa—"Tropical Medicine in Iowa in the Postwar Era";

Dr. Christian B. Luginbuhl, F.A.C.P., Des Moines, Iowa—"Acute Pulmonary Conditions Simulating Abdominal Disorders."

Dr. Lee R. Woodward, F.A.C.P., Mason City, President-Elect of the Society, delivered an address at the annual banquet.

Dr. Herman H. Riecker, F.A.C.P., Ann Arbor, Mich., spoke on "Heart Disease in Industry" at a Postgraduate Industrial, Medical and Surgical Conference held in Detroit, Mich., April 8, 1943, under the auspices of the Committee on Industrial Health of the Michigan State Medical Society and the Department of Postgraduate Medical Education of the University of Michigan.

Dr. Cornelius P. Rhoads, F.A.C.P., New York, N. Y., delivered the 9th Harrison Stanford Martland Lecture of the Essex County Anatomical and Pathological

Society of the Academy of Medicine of Northern New Jersey in Newark on March 17, 1943. Dr. Rhoads spoke on "Cancer and the Rôle Played by Vitamins and Endocrines."

On February 5, 1943, Dr. Harrison F. Flippin, F.A.C.P., Philadelphia, Pa., gave a Mayo Foundation Lecture in Rochester, Minn., on the "Management of Pneumonia."

Dr. George W. Thorn, F.A.C.P., Boston, Mass., gave the annual Alpha Omega Alpha Lecture at the Yale University School of Medicine, New Haven, Conn., February 11, 1943. The subject of Dr. Thorn's lecture was "Clinical Aspects of Disturbances in Sodium Chloride Metabolism."

On April 23, 1943, Dr. Chester M. Jones, F.A.C.P., Boston, Mass., delivered the 19th Lewis Linn McArthur Lecture of the Frank Billings Foundation, Chicago, Ill. Dr. Jones spoke on "The Relationship Between the Nervous System and Pain Perception with Particular Reference to the Gastrointestinal Tract."

The Northern Tri-State Medical Association held its annual meeting at Ann Arbor, Mich., April 13, 1943. Among the members of the College from the University of Michigan Medical School who participated in the program were:

Dr. Cyrus C. Sturgis, F.A.C.P.—"The Clinical Significance of Leukopenia";

Dr. Frank N. Wilson, F.A.C.P.—"The Diagnosis and Treatment of Coronary Artery Disease";

Dr. Herman H. Riecker, F.A.C.P.—"Differential Diagnosis and Management of Hypertension";

Dr. Richard H. Lyons (Associate)—"The Management of the Edematous Patient";

Dr. Arthur C. Curtis, F.A.C.P.—"The Treatment of Tinea Infections."

Dr. Irvine H. Page (Associate), Indianapolis, Ind., spoke on "Is Essential Hypertension of Renal Origin?" at a symposium on hypertension conducted at the annual meeting of the Hispanic-American Medical Society of New York, March 23, 1943, in New York, N. Y.

At the 97th Annual Meeting of the Ohio State Medical Association held in Columbus, March 30–31, 1943, Dr. Tom D. Spies, F.A.C.P., Birmingham, Ala., spoke on "Importance of Optimum Nutrition for the Civilian Population in Wartime" and Dr. John A. Toomey, F.A.C.P., Cleveland, Ohio, spoke on "Importance of Immunization of the Civilian Population in Wartime."

Dr. Walter F. Donaldson, F.A.C.P., Pittsburgh, Pa., was among those who addressed a session devoted to "Medicine and the War."

The Medical Association of the State of Alabama held its annual session in Birmingham, April 20–22, 1943. Among the speakers were:

Dr. James E. Paullin, F.A.C.P., Atlanta, Ga.—"The Contribution of American Medicine to the War Effort";

Bartholomew W. Hogan, F.A.C.P., Commander, (MC), U. S. Navy—"The Navy Medical Corps in Combat Areas."

Dr. Alexander H. Stewart, F.A.C.P., Harrisburg, has been reappointed Secretary of the Pennsylvania State Board of Health by the Governor.

Dr. Herbert T. Kelly, F.A.C.P., Philadelphia, Pa., presented a paper on "Nutrition—An Implement of the Physician" at a meeting of the Jefferson County Medical Society in Punxsutawney, Pa., April 8, 1943.

The 13th Annual Health Institute of the Woman's Auxiliary of the Philadelphia County Medical Society was held April 13, 1943. "Our Own Health" was the theme of the program. The following Philadelphia Fellows of the College contributed:

Dr. Truman G. Schnabel—"Is It Kidney?";
Dr. Merle M. Miller—"Influence of Allergy on Our Health";
Dr. Herbert T. Kelly—"Our Changing Foods";
Dr. George C. Griffith—"Care of the Heart—Normal and Abnormal."

Dr. John H. Musser, F.A.C.P., New Orleans, La., spoke on "The Doctor's Heart" at the annual meeting of the Arkansas Medical Society in Little Rock, April 19–20, 1943.

The 70th Annual Meeting of the Florida Medical Association was held in Jacksonville, April 15–16, 1943. Dr. George Baehr, F.A.C.P., Washington, D. C., spoke on "British and American Experiences in Civil Defense" and Sanford W. French, F.A.C.P., Colonel, (MC), U. S. Army, spoke on "The Doctor in the War Effort."

Dr. George W. Thorn, F.A.C.P., Hersey Professor of the Theory and Practice of Physic, Harvard Medical School, and Physician-in-Chief, Peter Bent Brigham Hospital, Boston, Mass., was awarded the "Chancellor's Medal" at the recent graduation ceremonies at the University of Buffalo. This medal is awarded annually by the University Council for "outstanding achievement."

Dr. Raymond Hussey, F.A.C.P., Baltimore, Md., spoke on "Occupational Diseases and Their Control" at a series of Industrial Health Institutes on the Conservation of Manpower conducted in Augusta, Savannah, Atlanta and Columbus, Ga., March 11–16, 1943. The program was sponsored by the Medical Association of Georgia, the Georgia Department of Health and the Associated Industries of Georgia.

Dr. Joseph F. Bredeck, F.A.C.P., St. Louis, Mo., conducted a discussion on syphilis and Drs. Carl V. Moore, Jr., F.A.C.P., and Raymond O. Muether, F.A.C.P, also of St. Louis, conducted a discussion on transfusions, at the annual session of the Missouri State Medical Association in St. Louis, April 18–20, 1943.

Dr. Harold W. Stevens, F.A.C.P., Middleboro, was recently elected President of the Massachusetts Public Health Association.

On February 16, 1943, the General Electric X-Ray Corporation, Chicago, Ill., was awarded the coveted Army-Navy "E" for high achievement in war production.

Dr. Cyrus C. Sturgis, F.A.C.P., Ann Arbor, Mich., gave the dedicatory address at the ceremonies dedicating the Institute of Medical Research at the Toledo Hospital, Toledo, Ohio, March 27, 1943. Dr. Sturgis spoke on "The Future of Medical Research."

The Institute for Medical Research was made possible by an endowment from the late Frank Collins of the National Supply Company of Toledo. The Institute

will maintain interest in diseases in general, depending upon the availability of the personnel and will not be devoted to the study of any single disease.

Dr. Clarence E. de la Chapelle, F.A.C.P., New York, N. Y., spoke on the "Treatment of Coronary Thrombosis" at a joint meeting of the Philadelphia Health Association and the Section on Medicine of the Philadelphia College of Physicians, May 10, 1943.

Dr. William S. McEllroy, F.A.C.P., Pittsburgh, Pa., spoke on the "Effect of the Army and Navy Collegiate Program on Medical Education" at a meeting of the Pittsburgh Surgical Society, March 25, 1943.

Return and Payment of Victory Tax by Employers

Employers are required to withhold the 5% Victory Tax on employees' wages in excess of $12.00 per week, and must make a return and transmit the tax quarterly to the Collector of Internal Revenue having jurisdiction, April 30, July 31, October 31 and January 31, using form V-1, Return of Victory Tax Withheld. This form may be obtained from the collector's office, and must be signed and sworn to by the employer. Duplicates of form V-2, receipt given employees, should be made and filed with the final report at the end of the year, on or before January 31, 1944. Because of severe penalties prescribed, physicians should make prompt returns on all tax withheld at the times designated.

War-Time Graduate Medical Meetings

By joint action of the American College of Physicians, the American Medical Association and the American College of Surgeons, an organization has been effected under the title of "War-Time Graduate Medical Meetings." Commander Edward L. Bortz, (MC), U.S.N., of Philadelphia, is the appointee of the American Medical Association and has been appointed Chairman. Dr. William B. Breed, of Boston, is the appointee of the American College of Physicians and Dr. Alfred Blalock, Baltimore, is the appointee of the American College of Surgeons.

After study of methods whereby medical authorities might be utilized in an educational program for the benefit of doctors in the armed services, Officials of the American Medical Association, American College of Surgeons and American College of Physicians have appropriated the sum of $20,000 and appointed a committee of three, one man from each organization, to proceed with the work of organization and action.

The program is essentially an elaboration of a teaching plan that has been used successfully in the Boston, Chicago and Philadelphia areas, originated by the American College of Physicians. It was so successful, in a limited way, that many requests have been received for its presentation on a national scale. In no way are the proposed courses to displace any of the educational activities now being carried on by the Officials of the Army and Navy medical services. The program has the approval, and is authorized by, Surgeon General James C. Magee, Surgeon General Ross T. McIntire and Surgeon General Thomas Parran.

The teaching schedule will include ward walks, clinics, practical demonstrations, moving pictures, lectures and conferences offered to medical installations throughout the entire nation.

In carrying out the plans of the Committee, no single pattern can be strictly followed. However, suggested methods of approach are herewith listed:

(a) Meetings such as those already held in Boston, Philadelphia and Chicago

where lecturers addressed groups in various camps on successive nights. Or, a one-day meeting at a central point with several outstanding speakers embracing topics of vital interest.

(b) The organization of teams which may arrange to visit one or more camps in nearby areas to put on a one-day and evening program. Such teams may appear at two or three adjacent camps on successive days.

(c) In areas where five or six service hospitals are within reasonable distance from a central distributing center, a complete six-day postgraduate program may be offered on the following basis:

The organization of six teams of two or more authorities each, from different medical specialties, to appear at the five or six hospitals in that area, each team on one particular day for five or six consecutive weeks. The program may include teaching ward rounds and laboratory demonstrations for small groups in the morning hours. Motion picture exhibits and one lecture with a question and answer period may be presented in the afternoon and a further lecture, seminar or round table conference in the evening.

It is evident that any of the above plans, all of which are tentative and illustrative only, might have to be modified to meet local conditions. However, teams of teachers should be available in the various medical concentration areas throughout the country to conduct full courses of instruction, where needed. Also, it may be expedient, at occasional intervals, to repeat this circular or peripatetic plan two or even three times per year, depending on the change of medical personnel in the service hospitals.

For organizational purposes, the country has been divided into 24 sections and key committees of three men appointed in each section to carry on the details of the program. Likewise, to insure a most worthwhile program, a group of qualified authorities is needed to serve as National Consultants in the various special fields.

The duties of the Section Committees are:

1. To be responsible for the details of programs at each Service hospital in their respective regions, where programs are to be conducted;
2. To be responsible for the selection of teachers and speakers, with the assistance of the Central Committee and of the National Consultants;
3. To arrange time of meetings and schedules for travel and appearance of the teachers within their respective territories;
4. To furnish copies of the program to the Commanding Medical Officers of the hospitals (programs shall be mimeographed or otherwise reproduced by the hospitals themselves);
5. Supervision of expenses, which shall be limited to necessary travel costs; also the forwarding of statements of same to the Secretary of the Central Committee, Dr. William B. Breed;
6. To obtain from the Commanding Officers at the end of the period of instruction a written statement concerning their impressions, and those of their staff, regarding the value of the courses, and suggestions for improvement.

The duties of the Consultants are:

1. Each Consultant to prepare a specimen six-hour teaching schedule, similar to the enclosed, which was prepared by Dr. Edward A. Strecker in the field of psychiatry;
2. To coöperate with the regional committees in working out local programs and securing the teachers.

When the teaching schedules have been prepared by the Consultants, and lecturers assembled, the programs will be submitted to the Surgeons General of the Army, Navy and Public Health Services and the Commanding Officers of the various Army Corps Commands and Naval Districts. When the desire for courses is in-

dicated, the details will be arranged through the local committee with the assistance of the key schedules and the appointment of speakers.

It is the desire of the organizations in charge to extend to the doctors in the armed services the best facilities of American medicine in the interest of our fighting men.

SPECIAL NOTICES

OFFICE OF CIVILIAN DEFENSE
Washington, D. C.
March 30, 1943

PENNANT TO IDENTIFY VEHICLES IN BLACKOUT

A uniform system of identification of emergency vehicles to enable them to operate during real or practice air-raid alarms was announced by the Office of Civilian Defense in Operations Letter No. 111, which is a supplement to Operations Letter No. 97.

The primary identifying device is a white pennant measuring 18 inches along each side with a 6-inch basic Civilian Defense insigne; that is, the letters CD in red inside a white triangle superimposed on a red circle. The pennant is to be attached to the left front portion of the vehicle.

To identify emergency motor vehicles at night, the Operations Letter further prescribes a headlight mask to be used over the right headlamp. This mask may be made of any opaque material that can be easily, quickly, and securely fastened to the headlamp. It is intended for use where blackout regulations permit the use of headlights; in coastal dimout areas it should be used in conjunction with dimout equipment. The design of the mask embodies the "CD" insigne 2½ to 3 inches in diameter in green.

Vehicles entitled to use the emergency identification include (a) vehicles of the armed forces of the United States or of her allies or other vehicles acting under orders or traveling with permission thereof; (b) vehicles of fire departments and governmental police agencies; (c) ambulances and rescue cars and other vehicles converted to such use in emergency services; (d) public utility repair vehicles operating in emergency service; (e) vehicles in emergency service as defined by State Civilian Defense authorities.

Use of the pennants and masks described was made mandatory for the 16 States and the District of Columbia in the Eastern Defense Command in an administrative order issued by the Director of Civilian Defense in accordance with the new Air Raid Protection Regulations which went into effect February 17. The Operations Letter recommends that all States adopt the definition of emergency motor vehicles and the methods of identification prescribed. Although many States have already adopted different methods of identifying emergency motor vehicles, it was urged that all States adopt the new devices. It was pointed out that a uniform system is particularly important in order that emergency motor vehicles which may be crossing State lines may not face unnecessary interference.

NURSES' AIDES FOR ARMY HOSPITALS

Volunteer Nurses' Aides trained under the joint program of the Office of Civilian Defense and the American Red Cross may now be used in Army hospitals, according to announcements from the two agencies.

The Surgeon General of the Army has requested this service, and the sponsoring agencies have recommended that Nurses' Aides be assigned to Army general or station hospitals on request of the Commanding Officer of the hospital. The Aides must receive their training in civilian hospitals as heretofore, however, and service in Army hospitals must not interfere with supplying Aides to civilian hospitals and health

agencies both now and in the event of enemy action, according to Medical Circular No. 28, issued by Dr. George Baehr, Chief Medical Officer, Office of Civilian Defense.

This proposed extension of the services of Nurses' Aides emphasizes the need for increased effort in recruitment in localities which have not yet participated in the program, the Circular pointed out.

CHANGES IN MEDICAL OFFICERS

Dr. A. William Reggio, Boston, recently State Chief of Emergency Medical Service for Massachusetts, has been appointed Regional Medical Officer for the First Civilian Defense Region, succeeding Dr. Dudley A. Reekie. Dr. Reggio, a graduate of Harvard Medical School, was formerly an instructor in surgery at Harvard Medical School; assistant visiting surgeon, Massachusetts General Hospital, and consulting surgeon at the Massachusetts Eye and Ear Infirmary. The First Region includes the New England States.

Dr. Reekie, who was assigned to the Central Office of the Medical Division in Washington in January as Acting Chief of the Field Casualty Section, has since been assigned by the Surgeon General of the U. S. Public Health Service to the U. S. State Department to head a group of Public Health Service officers who will act as special advisers on health matters to Robert Murphy, Chief Civil Affairs Officer for North Africa.

To succeed Dr. Reekie as Acting Chief of the Field Casualty Section, Dr. H. van Zile Hyde, Regional Medical Officer for the Second Civilian Defense Region (New York, New Jersey and Delaware), has been transferred to Washington. Dr. Hyde, formerly of Syracuse, New York, was the first Civilian Defense Regional Medical Officer appointed, having taken office in August 1941. Dr. John J. Bourke, deputy State Chief of Emergency Medical Service for New York, is now acting Regional Medical Officer for the Second Region.

Dr. David D. Rutstein, medical gas officer on the Washington staff, has resigned to become deputy health commissioner of New York City. Before he joined the Medical Division, Dr. Rutstein was chief of the cardiac bureau of the New York State Health Department, Albany, New York.

TRANSPORTATION PLANS FOR CIVILIAN DEFENSE

Transportation for casualties from scenes of disaster to hospitals and for injured persons or other patients removed from Casualty Receiving Hospitals to Emergency Base Hospitals are included in plans for emergency transport service during war disasters, described in recent Operations Letters issued by the Office of Civilian Defense.

Plans for local transportation are centered in the Transport Officer of the U. S. Citizens Defense Corps. It is the duty of the Transport Officer to maintain inventories of local equipment that can be used by the various emergency services of the Citizens Defense Corps, and he is responsible for organization, training, and supervision of volunteer drivers' units. Such equipment may include passenger cars, station wagons, motorcycles, ambulances, and other private vehicles. The instructions provide, however, that ambulances and cars or trucks used as improvised ambulances, with their drivers, should be assigned regularly to the Emergency Medical Service and be under its direction.

Through joint action of the Office of Defense Transportation and the Office of Civilian Defense, concurred in by the War and Navy Departments, local commercial motor vehicles, including taxicabs and trucks of small operators, which are now under the jurisdiction of the Office of Defense Transportation, have been released to and also are available to the Transport Officer for local service in case of war emergency. He may make use of such vehicles immediately, without application to the ODT.

For transport facilities needed outside the local area, such as might be required

for evacuation of civilians or for transfer of injured persons to Emergency Base Hospitals in other cities or rural areas, the OCD and the ODT are coöperating in the organization of motor transport units in the larger common, contract, and private motor carriers of the critical areas of the country. These units, which will be trained in convoy service, will be provided by the ODT on request of the local Commander of the Citizens Defense Corps through the State Transport Officer and proper ODT district managers. ODT is at present developing an organization in the critical areas of the country under which its district managers will make contact with the local Transport Officers to make certain that each community is organized to function under the plan.

Operations Letter No. 114, issued March 3, which describes the above arrangements, urges coöperative planning between the Citizens Defense Corps and such agencies as the American Red Cross, the Women's Defense and Ambulance Corps, and local or State automobile associations or clubs, in order that several agencies may not seek to mobilize the same equipment and drivers independently, but may do so in cooperation. It is pointed out, for instance, that most local Red Cross chapters have permanent transportation committees to provide motor transport facilities for disaster relief. By coöperative planning, such facilities can be made available also to the Citizens Defense Corps.

The Executive Board of the Catholic Hospital Association of the United States and Canada is pleased to announce that under the patronage and by the invitation of His Excellency, the Most Reverend Hugh C. Boyle, D.D., Bishop of Pittsburgh, a Wartime Conference of the Association will be held at the William Penn Hotel, Pittsburgh, Pennsylvania, Friday to Monday, June 11th to 14th, 1943.

Four Research Fellowships Available Through the New York Academy of Medicine

The Committee on Medical Education of the New York Academy of Medicine, 2 East 103rd St., New York City, has been entrusted with the award of four fellowships of $2,000 each for research in the following subjects:

1. The use of choline and other lipotropic factors in the prevention and treatment of fatty infiltration of the liver and hepatic insufficiency.
2. The action of ingested choline, lecithin, methionine and inositol on precancerous lesions and disorders associated with neoplastic disease.
3. The effects of riboflavin, certain amino acids, and casein on the development and growth of cancer.
4. Study of the relationship between precancerous lesions of the mouth, hepatic insufficiency and gastrointestinal disorders.

The funds for these Fellowships have been provided by Dr. Charles Mayer, of New York City.

The Committee requests that research workers, or laboratories engaged in studies along these lines or interested in research on these specified problems and who desire consideration by the Committee charged with awarding these fellowships, submit application for the desired award. This application should state the name of the individual who will conduct the research, the name of the laboratory or institution in which the work will be conducted, the special qualification, interest or attribute of the investigator and the institution which may justify the award. If the applicant has already conducted research in the specified field for which the award is sought, this fact should be stated and reprints of publications in this work by the author should accompany the application together with any other facts or information deemed pertinent. An approval of the director of the laboratory should accompany the application, if the application is not made by the director.

All applications should be sent in triplicate to Dr. Mahlon Ashford, Secretary of the Committee, not later than October 30, 1943.

Report: A. C. P. New Orleans Regional Meeting

The New Orleans Regional Meeting of the American College of Physicians, announced in the March issue of this Journal, was held on April 16–17.

The program was conducted at the Charity Hospital and consisted of a group of clinics on Friday morning, a General Session on Friday afternoon, and a group of clinics and a clinical pathological conference on Saturday morning. The program was of a high order, with timely topics and prominent authorities from civilian practice, from the Medical Corps of the Army, the Medical Corps of the Navy and other agencies. Dr. Edgar Hull, College Governor for Louisiana, was the General Chairman and the Governors of the participating States of Texas, Arkansas and Mississippi presided. A formal luncheon was held Friday noon, April 16, and was addressed by Comdr. E. L. Bortz, (MC), U.S.N.R., of Philadelphia, and by Col. W. Lee Hart, of the Medical Corps of the U. S. Army, Fort Sam Houston. There was a dinner meeting at the Roosevelt Hotel, Friday evening, April 16, at which Dr. John H. Musser was toastmaster. Addresses were made by Capt. Bertram Groesbeck, Jr., an envoy of the Surgeon General, U. S. Navy, Pensacola; by Col. Arden Freer, envoy of the Surgeon General, U. S. Army, Washington; and by E. R. Loveland, Executive Secretary of the College, Philadelphia.

Several of the important papers will appear in the Annals of Internal Medicine. The registration was considered excellent for a Regional Meeting, there being a total registration of 366, of which 139 were civilian physicians and 227 from the Army, Navy and Public Health Service.

Report: A. C. P. Washington, D. C., Regional Meeting

April 24, 1943

The Regional Meeting of the American College of Physicians for the District of Columbia, Delaware, Maryland, Virginia, West Virginia and North Carolina, announced in the March issue of the Annals of Internal Medicine, was held as scheduled and was up to this time the most largely attended Regional Meeting of the College. 203 Fellows, 60 Associates and 200 guest physicians, most of whom were medical officers of the Armed Forces, making a total of 463, were in attendance. Of this total, 263 were Service doctors and 200 were civilian doctors. The District of Columbia led with 142 physicians; Maryland had 120; Virginia, 100; North Carolina, 28; West Virginia, 14; Delaware, 8, and there were 51 additional men from 18 States outside of the region.

The program was of outstanding excellence, and many of the papers will later appear in this journal.

The entire group were guests of the U. S. Naval Hospital at luncheon and in the evening a dinner meeting was held at the new Statler Hotel. Dr. Wallace M. Yater, Governor for the District of Columbia, was toastmaster. The meeting was addressed by President James E. Paullin, Atlanta; Secretary-General George Morris Piersol, Philadelphia; Surgeon General Thomas Parran of the U. S. Public Health Service; Brigadier General Shelley U. Marietta, Commanding Officer of the Walter Reed General Hospital; Rear Admiral Charles W. O. Bunker, Commandant of the U. S. Naval Medical Center; Brigadier General David N. W. Grant, Air Surgeon of the U. S. Army Air Forces; Brigadier General James S. Simmons as personal representative of Surgeon General James C. Magee of the U. S. Army; Commander Edward L. Bortz, Chairman of the War-Time Graduate Medical Meetings, Philadelphia, and others.

OBITUARIES

DR. CHARLES WALTER WADDELL

Dr. Charles Walter Waddell, F.A.C.P., for thirty-six years a prominent physician in Fairmont, West Virginia, died at his home on Coleman Avenue, Monday morning, March 29, 1943, at the age of sixty-five. Dr. Waddell had been in declining health for more than a year, but continued to practice his profession until a few months ago when he was forced to relinquish his active duties, although his wise counsel and advice were sought thereafter by his patients and colleagues.

Dr. Waddell was born in Preston County, West Virginia, November 24, 1877. He graduated from West Virginia University in 1900 with an A.B. degree, then taught for three years in the Fairmont schools. He was graduated in Medicine from Harvard Medical School in 1907, and had practiced his profession in Fairmont since, devoting his time to diagnosis and internal medicine.

Dr. Waddell served his state and community in many ways. He was Chairman of the Advisory Board in World War I, was Consultant of the State Compensation Department and also of the Department of Public Assistance. He was very active in the Masonic and Elk Lodges.

In the year 1909 he married Miss Myrtle DeVene Shaw, a prominent singer of Fairmont. She survives him with three daughters.

Dr. Waddell was past President of the Marion County Medical Society, represented his District as a Medical Councillor in the State Association for many years and was President of the West Virginia State Medical Association in 1938. He was elected to Fellowship in the American College of Physicians in 1922 and became a Life Member of the College in 1937.

An illustration of the esteem in which Dr. Waddell was held in his home city is evidenced by the fact that the flag in front of the Fairmont General Hospital was placed at half mast when Dr. Waddell's death was announced, also the Elk's flag and flags on other public buildings were lowered to half mast.

ALBERT H. HOGE, M.D., F.A.C.P.,
Governor for West Virginia

DR. THEOPHILUS POWELL ALLEN

Dr. Theophilus Powell Allen (Associate), New York, N. Y., died at St. Luke's Hospital on January 27, 1943. He was born in Milledgeville, Georgia, on July 24, 1896. His preliminary education was at the Georgia Military College and he graduated from this school with first honors and as Captain of his Company.

He then entered the University of Georgia at Athens, and while there entered the World War, volunteering as a Private in the Coast Artillery at Fort Screven, Georgia, in January, 1918. From Fort Screven he was sent

to a training port at Fortress Monroe, where he received his commission as a Second Lieutenant in the Coast Artillery. He was then made Commanding Officer of a small artillery unit at Mayport, Florida, and was there when the Armistice was signed.

After the war he returned to the University of Georgia for a short time and then came to New York where he received his B.S. degree from Columbia University in 1921 and his M.D. from the College of Physicians and Surgeons in 1923.

After graduating, Dr. Allen interned at Bloomingdale Hospital, White Plains, N. Y., for six months. He then served two years medical internship at St. Luke's Hospital, ending in January, 1926. After this he spent eighteen months as intern at the New York Neurological Institute.

In 1926 he was married to Alma Helen Falbo, who survives him.

Dr. Allen was an Associate Attending Physician at St. Luke's Hospital and Assistant Attending Physician at the New York Neurological Institute. He was a member of the New York County Medical Society, The Medical Society of the State of New York, a Fellow of the New York Academy of Medicine and the American Medical Association, and an Associate of the American College of Physicians since 1939.

In spite of rheumatic endocarditis of many years' duration, Powell Allen was a most conscientious and tireless worker. He was a physician of outstanding ability and keen judgment and won the admiration and respect of all who knew him. He was particularly interested in allergic conditions and especially in food allergies, in which branch of medicine his work was outstanding. In addition, his knowledge of neurology was far beyond that of the average physician.

F. Warner Bishop, M.D., F.A.C.P.,
New York, N. Y.

DR. RALPH L. BYRNES

Dr. Ralph L. Byrnes, who was a Fellow of the American College of Physicians for 23 years, died of a heart attack at his home in Los Angeles on February 16 at the age of 64 years.

Dr. Byrnes was born at Walcott, Iowa. He was awarded the degree of M.S. at the State University of Iowa in 1906 and graduated the same year as M.D. at the College of Medicine of the same University. He did postgraduate work at Harvard University Medical School, Yale University, and the Army Medical School. He then moved to the West, and from 1911–1915 was Professor of Bacteriology and Pathology at the University of Utah. The remainder of his medical career was centered in and around Los Angeles, California, where he soon gained admirers by his unfailing devotion to the interests of his profession. He joined the faculty of the University of Southern California as Professor of Pathology, Bacteriology and Clinical Microscopy. He served in the First World War as Major

in the Medical Corps; was the founder of the Allied Post of the American Legion and a member of the Veterans Welfare Board. From 1919–1923 he was Professor of Diseases of the Chest at the College of Medical Evangelists, and for many years he was a member of the staff of the California Lutheran Hospital. Dr. Byrnes was a member of the Los Angeles County and California State Medical Associations and of the American Public Health Association.

During the last few years ill health compelled Dr. Byrnes to reduce his manifold activities, and with his death early this year medical circles in the vicinity of Los Angeles lost an ardent disciple and a colleague who was held in the highest esteem by his associates in Southern California.

Roy E. Thomas, M.D., F.A.C.P.,
Governor for Southern California

JOSEPH F. ELWARD

Dr. Joseph F. Elward of Plains, Pennsylvania, an Associate of the American College of Physicians, died February 6, 1943. He was born in Plains on July 4, 1890.

Dr. Elward, a teacher and a scholar, graduated as a Pharmaceutical Chemist in 1913 and as a Doctor of Pharmacy in 1915 from the Philadelphia College of Pharmacy and Science. He received his degree of Doctor of Medicine from Georgetown University in 1919. From 1924 to 1925 he received postgraduate training in radiology at the Boston City Hospital.

Since that time, Dr. Elward has held numerous positions. From 1927 to 1932 he was Associate Professor of Roentgenology at Georgetown University School of Medicine. From 1933 to 1942 he was Clinical Instructor in Radiology at the George Washington University School of Medicine. For many years, Dr. Elward was Roentgenologist at the Sibley Memorial, George Washington University and the National Homeopathic Hospitals in Washington, D. C. He was also Consulting Roentgenologist to the Gallinger, National Homeopathic and Freedmen's Hospitals.

Dr. Elward has contributed extensively to the medical literature, having written numerous interesting and worthwhile articles for publication.

He has been for many years an active participant in the medical world, having had membership in many national and local medical societies. He has served as Secretary of the American Therapeutic Society, as President and also as Secretary of the Georgetown Clinical Society and he is a former Secretary and former President of the Washington Medical and Surgical Society. His medical society memberships included the District of Columbia Medical Society, the American Roentgen Ray Society, the Radiological Society of North America, the American Association of Medical History, the American Association for the Advancement of Science, the American Association for the Study of Neoplastic Diseases.

He was a Fellow of the American College of Radiology and the Ameri-

can Medical Association. He was also a Diplomate of the American Board of Radiology and has been an Associate of the American College of Physicians since 1939.

It is with sincere regret that the passing of Dr. Joseph Elward, a renowned doctor of medicine, is acknowledged.

EDWARD L. BORTZ, M.D., F.A.C.P.,
Governor for Eastern Pennsylvania

DR. HARRY MYRREL STEWART

Dr. Harry Myrrel Stewart, F.A.C.P., died August 28, 1942, at the age of 66. He was born at Frankstown, Pa., 1876; graduated from Jefferson Medical College of Philadelphia in 1905, and for many years was Radiologist at the Mercy, Conemaugh Valley Memorial and Lee Homeopathic Hospitals. Dr. Stewart was a former President of the Cambria County Medical Society and of the Pennsylvania Radiological Society; a member of the Medical Society of the State of Pennsylvania, American Roentgen Ray Society and the Radiological Society of North America. He was a Fellow of the American College of Physicians (1920) and of the American College of Radiology. During World War I he served as Captain in the Medical Corps of the U. S. Army.

DR. ISEDOR MACK UNGER

Dr. Isedor Mack Unger, F.A.C.P., of Ithaca, N. Y., died October 20, 1942, at the age of 65. Dr. Unger received his medical training at Bellevue Hospital Medical College, 1898; interned at the Montefiore Hospital, 1898–1900, and thereafter did postgraduate study at the New York State Pathological Institute. He was a veteran of the Spanish-American War and World War I. He was formerly District Consultant to the Bell Telephone Company of New York. For the past several years he had been Consultant to the Tompkins County Memorial Hospital, Visiting Physician to the Cornell University Infirmary, and Chairman of the Tompkins County Citizens Military Training Camp. He was a Colonel in the Medical Officers' Reserve Corps of the U. S. Army and was Chairman of the Five-County Medical Advisory Board No. 41, New York Selective Service.

Dr. Unger was a member and past President of the Tompkins County Medical Society, a member of the Medical Society of the State of New York, the Association of Military Surgeons of the United States, a Fellow of the American Medical Association, and had been a Fellow of the American College of Physicians since 1929.

MINUTES OF THE BOARD OF REGENTS

PHILADELPHIA, PA.

APRIL 4, 1943

A meeting of the Board of Regents of the American College of Physicians was held in Philadelphia at the College Headquarters on April 4, 1943, convening at 10:00 a.m., with Dr. James E. Paullin presiding as President, Mr. E. R. Loveland acting as Secretary and with the following in attendance:

James E. Paullin .....*President*
Ernest E. Irons .....*President-Elect*
Charles H. Cocke .....*First Vice President*
Henry R. Carstens .....*Second Vice President*
A. Comingo Griffith .....*Third Vice President*
William D. Stroud .....*Treasurer*
George Morris Piersol .....*Secretary-General*
J. Morrison Hutcheson
Walter W. Palmer
O. H. Perry Pepper
T. Homer Coffen
Jonathan C. Meakins
Francis G. Blake
Reginald Fitz
Charles T. Stone
William B. Breed
Paul W. Clough .....*Acting Editor,* ANNALS
Edward L. Bortz .....*Chairman, Advisory Committee on Postgraduate Courses and Chairman of the Committee on War-Time Graduate Medical Meetings*

On motion by Dr. O. H. Perry Pepper, seconded and regularly carried, it was RESOLVED, that inasmuch as the Minutes of the preceding meeting of the Board of Regents have just been published in the ANNALS OF INTERNAL MEDICINE, their reading shall be dispensed with.

PRESIDENT JAMES E. PAULLIN: This meeting of the Board of Regents under ordinary conditions would occur at the annual meeting of the College, and at this time I would be the retiring President, and the honor and duties of the office would be assumed by most worthy successor, Dr. Ernest E. Irons. Because of conditions existing on account of the war, at the December meeting of the Board of Regents it was determined to abandon, for the time being at any rate, our annual meeting and all officers were requested to remain in their present status. I assure you that I profoundly appreciate the responsibilities and the obligations which have been placed upon me to carry on for another year as your President. These duties have been lightened because of the unselfish coöperation of Dr. Ernest E. Irons, the President-Elect, who has willingly given of his time and his talents in helping to further the interests and the activities of the College. The Board of Regents and the Board of Governors have been most helpful and the services of Mr. E. R. Loveland, Mr. Hegland, and of Miss Ott have made the duties falling upon me as light as possible. To all I am most grateful for your hearty coöperation.

Since the meeting of the Board of Regents in December I feel that the officials and the members should be informed of the activities of the College. The post-

graduate courses, which were planned and authorized for this year, have been carried out. The last course begins on April 5 under Dr. Chester Keefer in Boston. In the beginning some doubt was expressed as to whether the College was acting wisely in continuing these courses. The results of such activity, up to the present time, have been most gratifying. Every course has been oversubscribed and it is probable that if more had been arranged they could have easily been filled. For example, the course of Dr. Chester Keefer, although it does not begin until April 5, was oversubscribed in February, and it has been enlarged to accommodate eighty applicants instead of the original sixty. Other courses held in Rochester and Minneapolis have been equally as successful. Under conditions such as exist at the present time this experience should serve as an excellent example of the interest of the College and others in postgraduate medical training. It is believed that this type of instruction should be continued if possible during 1944.

Since the annual meeting of the College has been postponed, the Board of Regents recommended that Regional Meetings be held in different parts of the United States. So far Regional Meetings have been held in Philadelphia, Chicago and Boston. Other meetings are scheduled for New Orleans, Washington, Great Falls, Kansas City, Columbus and Jacksonville. It has been my pleasure to attend three of these meetings. The attendance has been all that could be expected. The interest of the members of the College, of the military, naval and civilian practitioners, has been quite gratifying. The type of papers presented and the enthusiasm of the authors in presenting their subjects have been most unusual. The meetings have been a great success and have served a very valuable purpose in advancing the ideals of the College towards the better training of our members in the practice of Internal Medicine. It is my belief that this one feature alone is a great contribution towards the advancement of medical education and to the furtherance of the ideals of practice in Internal Medicine.

A Committee has been appointed by the three medical organizations interested in graduate education to further the distribution of medical instruction on a much wider and a much more comprehensive basis than that which was contemplated originally by the American College of Physicians in its Regional Meetings. A resolution by Dr. Fitz gave your President authority to coöperate with other interested groups and to appoint a committee to further this purpose. It was believed that the American College of Physicians, in coöperation with the American College of Surgeons and the American Medical Association, could direct general courses of postgraduate instruction which could be offered through the Surgeons General of the Army, the Navy, and the Public Health Service to various military installations throughout the country, and to civilian physicians. This purpose has been accomplished. The American Medical Association appointed Dr. Edward L. Bortz, a member of its Council on Scientific Assembly; the American College of Surgeons appointed Dr. Alfred L. Blalock, Professor of Surgery at the Johns Hopkins Medical School, and the American College of Physicians appointed Dr. William B. Breed, Chairman of the Board of Governors, as a Central Committee to direct these activities.

For the first time, so far as I am aware, American Medicine, as represented by the American Medical Association, the American College of Physicians, and the American College of Surgeons, is attempting to formulate a program of graduate medical instruction to be given in various regions of this country. The combined effective strength of all three organizations is thrown into this undertaking with a realization that American Medicine owes an obligation to the physicians of the military forces and to civilian doctors who will not be able, because of increased local demands, to attend local meetings of either one of these associations, to have the benefit of this type of instruction. It is believed that this is a definite step in the advancement of scientific medicine and it is to be hoped that through such cordial,

sympathetic relationships that have been established between these organizations, a program which is just now beginning to be formulated will continue in its great usefulness, not only during the period of the present emergency but perhaps it will make its usefulness known to such an extent that it will be continued hereafter.

The Executive Committee of the College appointed a Committee on Planning for War and Post-War Medical Services. This Committee consisted of Dr. Walter W. Palmer, Chairman, Dr. William B. Breed, Dr. Edward L. Bortz, Dr. Ernest E. Irons and Dr. George Morris Piersol, with your President as ex-officio member. A similar Committee appointed by the American College of Surgeons consisted of Dr. Irvin Abell as Chairman, Dr. Evarts A. Graham, Dr. Frederick Coller, Dr. Arthur Allen and Dr. James Mason as members. These Committees will act in a consultative and advisory capacity on medicine, surgery and other topics, with a Central Committee nominated by the Board of Trustees of the American Medical Association, consisting of Dr. Roger I. Lee, Chairman, Dr. Fred W. Rankin, Dr. Harrison H. Shoulders and Dr. James E. Paullin. Perhaps other members will be added to the latter committee.

The Committee on War and Post-War Medical Services, after completing its organization and establishing its various subcommittees in the branches of medicine, surgery and allied specialties, will be composed of men who represent the outstanding thought of the professions in the United States. It will be able to formulate a plan and assume its responsibility in providing sound advice and leadership to any group of individuals who have the real interest of the world at heart in any post-war medical effort that must of necessity be made by the people of the United States after peace is declared. There are many problems which must be considered by this Committee because of our extensive commitments. We must at all times be mindful of the great sacrifice which every physician is making who enters the armed service. This sacrifice is made not only by doctors but by other individuals who volunteer for service. In planning, however, for physicians during the war effort, it is necessary that the newest and latest knowledge of diagnosis and treatment be immediately transmitted to our men in the military services. We should bear in mind that during the present war and after a declaration of peace it will be necessary for many physicians who have served either in tactical units, or in the theater of operations, to have refresher courses in medicine and surgery before returning to general practice. Such should be a privilege extended these men by our government.

A Post-War Planning Committee should select as members of its various subcommittees on post-war medical services physicians who will be willing to give of their time and effort and who will be willing to go as emissaries to foreign countries in order to render medical care. Many of our members who are physically disqualified for military duty, and some who are retained in essential capacities, will help in this undertaking. With the end of the war and the return from military service of younger men, many of those who now occupy essential positions and those who are physically disabled, but capable of active work, can volunteer for this type of non-military service, thus allowing their places to be filled in teaching and other civilian needs by men recently returned from military duty.

The College of Physicians, with other medical groups, participated in sponsoring a conference held in New York in March, under the auspices of the Finlay Institute of the Americas. It is believed that our sponsoring of this activity was of considerable benefit to the members of our organization, and it is hoped that as a result of this conference a sufficient amount of interest was aroused among medical men to go forward with the completion of a program to render this particular type of service.

It is believed that such activities of the American College of Physicians are a distinct part of our obligations to American Medicine and we desire to continue to be of the utmost service to our country and to the military forces in the present emergency.

PRESIDENT PAULLIN: The Secretary will kindly present the communications.

SECRETARY LOVELAND: I have received letters from Drs. Barr, Webb, Churchill, Tenney, Lee and Morgan, expressing their disappointment at not being able to be present at this meeting and sending their greetings to the Board. I have another communication to the Regents from Acting Governor J. Edwin Wood of Virginia, who recommends that the Regents provide a clearer statement of the qualifications for Associateship.

(Reads letter from Dr. Wood.)

The Credentials Committee will probably report on recommendations later in this meeting. I have another communication from Governor Edward L. Bortz, suggesting a plan by which the Governors shall follow up all Associates in an effort to see that each Associate shall do the necessary work to qualify for Fellowship.

(Reads letter from Dr. Bortz.)

PRESIDENT PAULLIN: Gentlemen, you have heard the communication from Dr. Bortz. What is your pleasure? Would you like it referred to the Chairman of the Committee on Credentials?

DR. PALMER: I hope the Regents will consider it. I happen to be one of those individuals who is opposed to regimentation and I think that if the suggestion is put in a different manner—as an opportunity rather than as a "must," I would be more in favor of it. There are men associated with teaching centers where their opportunities for advancement in their field is far greater than would be obtained by attending a graduate course organized by the College.

DR. IRONS: I think it a fine idea to have Governors given an additional opportunity to father the younger men. I don't think there should be any "must," however, but more of an expression of interest and a hope that the educational progress of these young men will continue. The American Board says, "Here is something you should do if you want to do a good job."

DR. BREED: What attitude should the College Governor take toward recruiting new members in his State? Formerly I took the attitude that it was unwise to proselytize for the College and that we would probably get better men if, through our activities, we make it attractive to them rather than to seek them out. There are other Governors, however, who have a different attitude. I am a bit in doubt as to what the proper attitude should be. It is an important problem that I think worth discussing.

DR. COCKE: Having been a Governor for a long time, I had an entirely different point of view from Dr. Breed. In a community of large teaching centers of medicine such an attitude is not only understandable but valuable, because young men by their own initiative and interest are trying to advance, and are aligned with various institutions affording such opportunities. But, take such a State as North Carolina; I think it is distinctly the Governor's duty and obligation to know who are the up and coming young men in his State and to try to stimulate their interest in such an organization as the College. In our State we were early in organizing Regional Meetings; we encouraged and frequently invited these men as our guests to our Regional Meetings and we attempted to stimulate their interest.

SECRETARY LOVELAND: In regard to stimulating Associates to qualify for Fellowship, I would remind the Board that every Associate of the College receives each year a questionnaire on which he records what he has accomplished during the year—publications, advancements in appointments, postgraduate courses taken, new society memberships, etc. This was initiated by the Board as a plan to show we are interested in following each Associate in his effort to qualify for Fellowship.

PRESIDENT PAULLIN: Gentlemen, if there is no objection, may this letter from Dr. Bortz be referred to the Committee on Educational Policy for consideration, with direction to report back to this Board at its next meeting?

(A motion to refer the letter to the Committee on Educational Policy was made by Dr. Piersol, seconded by Dr. Griffith, and carried.)

PRESIDENT PAULLIN: May we have the report of the Secretary-General, Dr. George Morris Piersol.

DR. PIERSOL: We herewith report the deaths since the last meeting of this Board of the following fourteen Fellows and two Associates:

Fellows

Bonney, Sherman Grant	Denver, Colo.	November 19, 1942
Byrnes, Ralph L.	Los Angeles, Calif.	February 16, 1943
Dennison, Archibald S.	Lynn, Mass.	January 22, 1943
Elliott, Jabez H.	Toronto, Ont., Canada	December 18, 1942
Freeman, Elmer Burkitt	Baltimore, Md.	December 23, 1942
Kruse, Fred Herman	San Francisco, Calif.	January 14, 1943
Layton, Oliver M.	Fond du Lac, Wis.	December 27, 1942
Porter, Ernest Boring	Altadena, Calif.	November 15, 1942
Rowland, Peter Whitman	Memphis, Tenn.	January 10, 1943
Stofer, John William	Gallup, N. M.	January 16, 1943
Watkins, Fonso Butler	Morganton, N. C.	March 9, 1943
Wilmer, Harry B.	Philadelphia, Pa.	January 16, 1943
Woltmann, Harro	Mansfield, Ohio	December 27, 1942
Work, Hubert	Englewood, Colo.	December 14, 1942

Associates

Allen, Theophilus Powell	New York, N. Y.	January 27, 1943
Elward, Joseph Francis	Plains, Pa.	February 6, 1943

We also report the following new Life Members since the last meeting of this Board, bringing the grand total to 211, of whom 22 are deceased, leaving a balance of 189:

Charles L. Hess	Bay City, Mich.
Ralph King Hollinshed	Westville, N. J.
Ranald E. Mussey	Troy, N. Y.
Gabriel B. Kramer	Youngstown, Ohio
Eliah Kaplan	New Castle, Pa.
Spencer Augustus Folsom	Orlando, Fla.
Robert A. C. Wollenberg	Detroit, Mich.
Edgar F. Kiser	Indianapolis, Ind.
William Corr Service	Colorado Springs, Colo.
Harry Gauss	Denver, Colo.
Harold E. Himwich	Albany, N. Y.
Willard Boyden Howes	Detroit, Mich.
Jesse D. Riley	State Sanatorium, Ark.
Joseph C. Placak, Sr.	Cleveland, Ohio
Harold R. Roehm	Birmingham, Mich.
Charles S. Bluemel	Denver, Colo.
George E. Baker	Casper, Wyo.
Samuel A. Loewenberg	Philadelphia, Pa.
Vernon C. Rowland	Cleveland, Ohio
Frederick Slyfield	Seattle, Wash.
Roy Colonel Mitchell	Mount Airy, N. C.
John T. Murphy	Toledo, Ohio
Harold Orr	Edmonton, Alta., Canada
V. Thomas Austin	Urbana, Ill.

We also report that the College membership "as of March 14, 1943" was:

Masters	4
Fellows	3,829
Associates	1,127
Grand Total	4,960

An analysis of the number of members serving in the Armed Forces at this date is as follows:

	Fellows	Associates	Total
Army	605	346	951
Navy	261	100	361
U. S. Public Health Service	34	21	55
	900	467	1,367

This is 27.55 per cent of the entire College membership. Seven members have been reported missing in action or their whereabouts as yet not established.

We report the following members delinquent in dues for two or more years and therefore, under the Constitution and By-Laws, subject to being dropped at this time:

(Reads list of five names.)

PRESIDENT PAULLIN: You have heard the report of the Secretary-General. May I particularly call your attention to the names of two deceased Fellows who in the past had an eminent part in the activities of the College, namely, Dr. Jabez Elliott, Toronto, who was a former Vice President and a former Governor of the College, and Dr. Harry B. Wilmer, Philadelphia, who has occupied various posts in the College and was at the time of his death a member of the House Committee.

SECRETARY LOVELAND: I should like to suggest a period of thirty days' grace for the entire list of delinquent members. This will give any Regent or Governor a further opportunity to contact these men and thus to give them a second chance. All of them have been communicated with on numerous occasions.

(Motion was made and seconded that the four men on the delinquent list be given a thirty-day grace period in which to pay their dues; if not paid at that time, their names will be automatically dropped from the roster. Motion was put and carried.)

(Motion was made, seconded and carried to accept the report of the Secretary-General as a whole.)

PRESIDENT PAULLIN: We shall now have reports of committees and matters of new business. Dr. Ernest E. Irons, Chairman, will report from the American Board of Internal Medicine.

DR. IRONS: Mr. President, I have no formal report because the annual meeting of the American Board will not be held until the latter part of May or June, probably in Philadelphia. Contrary to our expectations, applications for examination have not decreased, but greatly increased. At the October examination we had somewhat over three hundred examinees and in February the number was between one hundred and two hundred. This shows what a load members of the Board are carrying, and I want to express here my very great appreciation for their unfailing diligence. In October we held examinations in twenty-eight cities and in thirty-four camps and station hospitals in this country. I think the men in the camps appreciated this cooperation and expression of interest of the Board in their welfare. In addition, we have held examinations in Puerto Rico, Honolulu and North Africa. We have plans for examinations in Australia and in India. The Surgeon General of the Army has offered coöperation in getting the questions distributed to foreign regions through

use of the diplomatic pouch. I also wish to commend with pleasure the excellent services of the Acting Secretary of the Board, Dr. William A. Werrell of Madison; he has carried on exceedingly well in the absence of Dr. Middleton.

The standards of the Board have been maintained at the level that we had attained before the war and we propose to hold them so. There were 25 per cent failures on the last written examination and 25 per cent failures among the remainder on the oral examination. Regional oral examinations will be held for this country as soon as we can get final returns from the February examination. These regional oral examinations will replace the oral examinations that customarily were given at the annual meetings of the American College of Physicians and the American Medical Association. Certain difficulties with regard to the sub-specialties in medicine have been overcome, sources of irritation have been adjusted and we now have a group of coöperating sub-specialty committees.

I want to express the Board's very great gratification of the nomination and subsequent election of Dr. James J. Waring to membership on the Board.

(Motion to accept Dr. Irons' report was made, seconded and carried.)

PRESIDENT PAULLIN: Next is a report of the Committee on Fellowships and Awards by Dr. Francis G. Blake, Chairman.

DR. BLAKE: Dr. Rulon W. Rawson, one of our research fellows working with Dr. Means at the Massachusetts General Hospital, completed that fellowship some months ago and has submitted a very satisfactory report on the studies he has been making, and he will continue in Dr. Means' clinic this coming year. He states that his work under Dr. Means has been most profitable and Dr. Means has been most helpful; he expresses his thanks to the Regents and members of the American College of Physicians for granting him this fellowship.

There are still two active research fellows at work—Dr. Carl G. Heller, working under the direction of Dr. Myers at the Wayne University College of Medicine, and Dr. James Hopper, Jr., working on various methods of measuring blood volume under Dr. Peters at Yale University School of Medicine. . . .

Dr. Hopper has lived up to his recommendations when he came from Dr. Kerr in California. He will complete his fellowship at the end of August, and Dr. Kerr has offered him an appointment as Instructor in Medicine at the University of California on the completion of his fellowship in New Haven.

(Motion was made by Dr. Stroud, seconded and carried, accepting the above report.)

PRESIDENT PAULLIN: Dr. Piersol will report for the Committee on Credentials.

DR. PIERSOL: A full meeting of the Committee on Credentials was held April 3 and the following action taken:

1. The Chairman and the Executive Secretary were directed to draw up a clarification of the published requirements for Associateship, especially with regard to fundamental training that will be necessary for an Associate to qualify for certification within the specified time limits;

2. The Committee agreed in the case of candidates from Canada to accept in lieu of certification by the American Boards equivalent certification in Canada, such as fellowship in the Royal College of Physicians or certification by that College if, as and when such is established on at least an equivalent basis with that in the United States;

3. The Committee reviewed the credentials of one hundred candidates for Fellowship and in accordance with the mimeographed lists that have been distributed to the Board recommends the election of seventy-seven, of whom three were for direct Fellowship, three were physicians who had previously served a five-year Associate term in good standing but had not completed the requirements at the expiration of their terms and consequently had been dropped, and four were

advanced to Fellowship as of December, 1943. Three candidates for direct Fellowship were recommended for election first to Associateship, seventeen candidates were deferred for further credentials and three candidates were rejected altogether;

4. The Committee reviewed the credentials of seventy-four candidates for Associateship, mimeographed list of whom is in your hands. Sixty-two were recommended for election, eleven were rejected and one was deferred for further credentials;

5. An analysis of the class of Associates elected on April 3, 1938, whose terms expire at this time, is as follows:

Qualified for Fellowship	111
Deceased	2
Resigned	1
Dropped for failure to qualify in maximum term	5
Deferred until after the war because of military service	10
Total	129

Eighty-six per cent of that group have qualified for Fellowship.

6. The following five practicing physicians have not qualified within the five-year period and under the By-Laws must now be dropped:

(Reads list of names.)

7. The following group of ten Service physicians have not qualified for Fellowship, but because they are on active military duty their Associate terms may be extended until after the war:

(Reads list of names.)

(On motion of Dr. Pepper, seconded by Dr. Stone and unanimously carried the report and recommendations of the Credentials Committee were accepted and approved, after adoption of each section individually.)

The following seventy-three physicians, therefore, were elected to Fellowship as of April 3, 1943:

Anderson, James Fleming, Los Angeles, Calif.
Anderson, William Arnold Douglas, St. Louis, Mo.
Appelbaum, Emanuel, New York, N. Y.
Baker, Wyrth Post, Washington, D. C.
Banyai, Andrew Ladislaus, Wauwatosa, Wis.
Barnes, Maurice C., Waco, Tex., (MRC), U. S. Army
Barnes, Wayne Clifton, Springfield, Mass.
Beber, Meyer, Omaha, Nebr.
Benjamin, Samuel, Washington, D. C.
Bennett, Thomas Wade, Columbia, S. C., (MC), U. S. Naval Reserve
Bloch, Robert Gustav, Chicago, Ill.
Bloom, Meyer, Johnstown, Pa.
Bohorfoush, Joseph George, Madison, Wis., (MRC), U. S. Army
Brandstadt, Wayne Glassburn, (MC), U. S. Army
Brewer, Kenneth Arthur, (MC), U. S. Army
Bromberg, Leon, St. Louis, Mo., (MC), U. S. Naval Reserve
Brosnan, James Timothy, Worcester, Mass.
Brumm, Harold J., St. Joseph, Mo.
Carey, Lawrence Sherwood, Philadelphia, Pa.
Carl, Louie Tate, Jackson, Miss., (MRC), U. S. Army
Coffin, George Jarvis, New York, N. Y.
Crager, Jay Cecil, Beaumont, Tex.
Dufault, Paul, Rutland, Mass.

Eaton, Hamblen Cowley, Harrisburg, Pa., (MC), U. S. Naval Reserve
Edson, Reginald Campbell, West Hartford, Conn.
Elliott, Clarence Kilgore, Lincoln, Nebr.
Farber, Jason Engels, Buffalo, N. Y.
Filberbaum, Milton Bayard, Brooklyn, N. Y., (MC), U. S. Naval Reserve
Flood, Charles Albert, New York, N. Y., (MRC), U. S. Army
Gilbert, James Thomas, Jr., Bowling Green, Ky., (MRC), U. S. Army
Goldberg, Harold Herbert, Newark, N. J.
Gregg, Frank John, Pittsburgh, Pa.
Healy, Thomas Charles, Argyle, N. Y.
Herring, Albert Crawford, New York, N. Y.
Hollingsworth, Merrill Windsor, Santa Ana, Calif.
Hunnicutt, Thomas Nathaniel, Jr., Newport News, Va.
Johnstone, Benjamin Irvine, Detroit, Mich.
Josey, Allen Izard, Columbia, S. C., (MRC), U. S. Army
Kehl, Kenneth Charles, Racine, Wis.
Keller, William Karl, Louisville, Ky., (MC), U. S. Naval Reserve
Kendall, Ralph Emerson, Hartford, Conn.
Levan, John Boyer, Reading, Pa., (MRC), U. S. Army
Lundy, Clayton Jackson, Chicago, Ill., (MRC), U. S. Army
Markowitz, Benjamin, Bloomington, Ill.
Marks, Jerome Alexander, New York, N. Y.
Marty, Frederick Nicholas, Syracuse, N. Y.
Mayer, Joseph Ralph, Rochester, N. Y.
McCauley, Lewis Ross, Punxsutawney, Pa.
Miller, Malcolm White, Philadelphia, Pa.
Molyneux, Arthur Van Horn, Honolulu, T. H.
Muether, Raymond Oliver, St. Louis, Mo.
Mufson, Isidor, New York, N. Y.
Ormond, Allison Lee, Black Mountain, N. C.
Phelps, Maxwell Overlock, Hartford, Conn.
Rutledge, David Ivan, Boston, Mass., (MRC), U. S. Army
Salley, Samuel Marion, Miami, Fla., (MRC), U. S. Army
Saslow, Benjamin I., Newark, N. J.
Schnatz, Frederick Theodore, Buffalo, N. Y.
Schwedel, John Bernard, New York, N. Y., (MC), U. S. Naval Reserve
Schweitzer, Harold Theodore, Buffalo, N. Y.
Skinner, Norman Stewart, St. John, N. B., Can.
Soloff, Louis Alexander, Philadelphia, Pa.
Steinberg, Charles LeRoy, Rochester, N. Y.
Torbert, Harold Chester, San Diego, Calif.
Traub, David Strouse, Louisville, Ky., (MRC), U. S. Army
Tyler, Richard Smith, Cincinnati, Ohio
Wall, Emmett Daniel, Peoria, Ill., (MRC), U. S. Army
Wilkinson, George Richard, Greenville, S. C.
Williams, Byard, New York, N. Y.
Williamson, Charles Grant, Brooklyn, N. Y.
Wilson, Olin Glenwood, Canton, Ohio, (MRC), U. S. Army
Wilson, Walter John, Jr., Detroit, Mich., (MRC), U. S. Army
Wright, Willis Dean, Omaha, Nebr., (MC), U. S. Naval Reserve

The following four physicians were elected to Fellowship as of December, 1943:

Hughes, John Davis, Memphis, Tenn., (MRC), U. S. Army
Jones, Charles Alexander, Philadelphia, Pa., (MC), U. S. Naval Reserve

Winn, William Alma, Visalia, Calif.
Wise, Irvin Milton, Mobile, Ala.

The following sixty-five physicians were elected to Associateship as of April 4, 1943:

Acosta-Velarde, Antonio, Arecibo, P. R.
Allen, Glen Ivan, Peoria, Ill., (MRC), U. S. Army
Allen, Irene Viola, East St. John, N. B., Can.
Bell, George Olaf, Waban, Mass.
Berberich, Walter Francis, (MC), U. S. Navy
Bettison, William Leslie, Grand Rapids, Mich., (MRC), U. S. Army
Bleecker, Philip Bernard, Memphis, Tenn., (MRC), U. S. Army
Brink, James Russell, Grand Rapids, Mich., (MC), U. S. Naval Reserve
Bruckman, Frederick Sweet, San Francisco, Calif., (MRC), U. S. Army
Buis, Lester James, Richmond, Va.
Burns, Frederic Joseph, Providence, R. I.
Butler, Stuyvesant, Winnetka, Ill.
Carlisle, Margil Clinton, Waco, Tex.
Carter, Harold Robert, Denver, Colo.
Chapman, Asher Spafford, Rochester, Minn.
Chisholm, Donald Raymond, Kealia, Kauai, T. H.
Craddock, George Barksdale, Lynchburg, Va., (MRC), U. S. Army
DeLaureal, Thomas Hugh, Lake Charles, La.
Edger, Herbert Downing, (MC), U. S. Army
Eigenbrod, Frederick August, New Orleans, La., (MRC), U. S. Army
Ellinger, George Frederick, Honolulu, T. H., U. S. Public Health Service
Fischl, Arthur Allyn, Long Island City, N. Y.
Foret, Marcel Jean, New Orleans, La., (MRC), U. S. Army
Garcia, John Edward, New Orleans, La., (MRC), U. S. Army
Gill, Charles Chute, (MC), U. S. Army
Goldman, Bernard Alvin, New Orleans, La., (MRC), U. S. Army
Gordon, Abraham Maury, New Orleans, La., (MRC), U. S. Army
Goyette, Edwin Matthew, (MC), U. S. Army
Hanford, Russell Bratton, Oakesdale, Wash., (MRC), U. S. Army
Hanlon, Thomas Joseph, St. Louis, Mo., (MRC), U. S. Army
Hedges, Robert Nathaniel, Chicago, Ill.
Hoffman, Reuben, Henryton, Md.
Hollander, Joseph Lee, Philadelphia, Pa., (MRC), U. S. Army
Kapernick, John Stuart, Rochester, Minn., (MRC), U. S. Army
Kaplan, Murrel Herman, New Orleans, La., (MRC), U. S. Army
Katz, Kermit Harry, Dorchester, Mass.
Kramer, Milton Lurie, New York, N. Y., (MRC), U. S. Army
Layne, John Anthony, Great Falls, Mont.
Leslie, Alan Noah, New York, N. Y., (MC), U. S. Naval Reserve
Lovell, Harold William, New York, N. Y.
Mansmann, James Andrew, Pittsburgh, Pa.
Marino, Frank Xavier, New Orleans, La.
Morris, Harold Thoes, Topeka, Kan.
Pedigo, George William, Jr., Louisville, Ky.
Pesquera, Gilberto Severiano, Mount McGregor, N. Y.
Powell, George Merle, (MC), U. S. Army
Roberts, Charles James, Enid, Okla., (MRC), U. S. Army
Rogers, Howard Milton, St. Petersburg, Fla.
Rosenblum, Louis A., Forest Hills, L. I., N. Y.

Rothman, Theodore, Paterson, N. J.
Shaffer, Carl Francis, Detroit, Mich.
Shipp, Leland Parmater, Battle Creek, Mich.
Skinner, Robert Barrett, (MC), U. S. Army
Smart, Reginald Hughes, Los Angeles, Calif.
Stein, William, New Brunswick, N. J., (MRC), U. S. Army
Stevens, Joseph Blackburn, Greensboro, N. C., (MRC), U. S. Army
Strong, Paul Stone, Baltimore, Md., (MRC), U. S. Army
Swanson, Paul Richard, Chattanooga, Tenn., (MRC), U. S. Army
Thompson, Charles Middleton, Philadelphia, Pa., (MC), U. S. Naval Reserve
Ullman, Robert Adolph, Buffalo, N. Y.
van Ravenswaay, Arie Cornelius, Boonville, Mo., (MRC), U. S. Army
Walsh, Bernard John, Washington, D. C.
Whims, Clarence Bernard, Ventnor City, N. J., (MRC), U. S. Army
White, Major Samuel, (MC), U. S. Army
Zimmerman, Solomon Lincoln, Columbia, S. C.

(Dr. Charles H. Cocke, First Vice President, takes the Chair.)

DR. PAULLIN: In the absence of Dr. Lee, I was asked to make a report for the Committee on Public Relations.

The Committee on Public Relations of the College met at the College Headquarters at 3:00 p.m., Saturday, April 3, 1943, with the following members present: Dr. A. C. Griffith, Dr. J. Morrison Hutcheson and Dr. James E. Paullin, Acting Chairman. Drs. Roger I. Lee and David P. Barr were unable to be present.

The Committee recommends:

(1) That the resignation of Dr. E. J. Engberg, F.A.C.P., Faribault, Minn., be accepted;

(2) It is recommended that the dues of —. —— —. ————, F.A.C.P., be waived for the years 1942 and 1943 due to illness, and that his check be returned.

It is recommended that the Secretary transmit to him the best wishes of the Board of Regents for a speedy recovery.

(3) The communication of Dr. C. O. Bailey, F.A.C.P., Los Angeles, Calif., concerning the establishment of an American Board of Medical Educators for the purpose of improving the teaching of medical subjects in medical colleges be referred to the Association of American Medical Colleges, without recommendation from this Committee. It is the belief of the Committee on Public Relations that matters relating to medical teaching are more of a problem of the Association of American Medical Colleges than that of the American College of Physicians.

Respectfully submitted,
Dr. A. C. GRIFFITH
Dr. J. MORRISON HUTCHESON
Dr. JAMES E. PAULLIN, Acting Chairman

(The above report was accepted section by section and by motion, made, seconded and carried, the report as a whole was approved.)

(Dr. Paullin resumes the Chair.)

PRESIDENT PAULLIN: The next item on the agenda is the report of the Advisory Committee on Postgraduate Courses by Dr. Edward L. Bortz, Chairman.

DR. BORTZ: Mr. President, under the auspices of the College three courses in Internal Medicine have been offered this past winter. The first course was at the University of Minnesota, January 25–30, in which the published maximum registration was 50, but in which 77 men were accommodated. Of these 32 were Fellows of the College, 17 Associates and 28 non-members. Nine of the registrants were from the military Services.

The second course was given at the Mayo Clinic under Dr. E. H. Rynearson, February 1–6, in which the maximum published facilities were 50, but in which 58 were finally accommodated. Of this group 32 were Fellows, 16 Associates and 10 non-members. Nine of the registrants were from the military Services.

The third course, under Dr. Chester S. Keefer at Boston University, April 5–10, had published maximum facilities for 50, but accommodations have been provided for a total of 82. Of these 38 are Fellows of the College, 20 Associates and 24 non-members. 26 registrants are from the military Services.

The College, through these courses, has created opportunity for serious graduate study for 217 doctors. We staggered these courses so that members could take more than one course if desired. Several members took advantage of this opportunity and two members registered for all three courses. It is the thought of the Committee that in the future we shall follow the staggering system, making these facilities available to all members. What the future holds for these courses, of course no one can say, but there appears to be a very healthy interest among a considerable number of men, among members of the College and also among physicians who are looking forward to membership in the future.

The Committee recommends that certain courses be offered next autumn, including a course in Allergy of one week's duration at the Massachusetts General Hospital under Dr. Francis Rackemann; a course in Diseases of the Endocrine System of one week's duration, in Chicago, under Dr. Willard Thompson; a course in Special Medicine, two weeks' duration, in Philadelphia, with subjects divided somewhat along the following lines:

One day's instruction in Neuropsychiatry
One day's instruction in Cardiovascular Problems
One day's instruction in Gastrointestinal Disorders
One day's instruction in Problems of Cancer
One day's instruction in Metabolism
One day's instruction in Treatment of Shock, Plasma and the Protein Fractions of Blood, etc.;

a course in General Medicine, one week's duration, at the University of Michigan under Dr. Cyrus Sturgis; and possibly a course in General Medicine of one week's duration, in San Francisco, although this latter suggestion will require further consideration and investigation.

(A motion to accept the above report was made by Dr. Stone, seconded and carried.)

DR. PEPPER: What is the explanation, Dr. Bortz, of these large numbers of men taking the courses, considering present existing conditions of shortages of doctors and overwork of doctors? What are these men doing and how do they get away?

DR. BORTZ: We were surprised to find so large a registration. Many of them are in the Armed Forces already. Others perhaps take advantage of these courses to get a brief vacation from practice. I do not know anything more.

PRESIDENT PAULLIN: Dr. Irons will now give a report of the Committee on Educational Policy.

DR. IRONS: We met with Dr. Bortz' Committee on Postgraduate Courses yesterday, and Dr. Bortz has already covered the activities quite thoroughly. The Committee on Educational Policy has been concerned with the organization of this joint activity of American medicine, The War-Time Graduate Medical Meetings; also in the program President Paullin outlined at the beginning of this meeting concerning the activities of the College along with other organizations in preparing for post-war opportunities for physicians returning from the Service. This Committee is actively interested in the entire program and is in agreement with the matters that have been proposed.

(Motion to accept report of the Committee on Educational Policy was made by Dr. Pepper, seconded by Dr. Palmer and carried.)

PRESIDENT PAULLIN: Next is the report of the Chairman of the Board of Governors, Dr. William B. Breed.

DR. BREED: Mr. Chairman, members of the Board of Regents: It is quite obvious that I can give you no definite report from the Board of Governors because that Board has not met since your last meeting, nor have I as yet functioned as Chairman of the Board because there has been no meeting since my election to office. However, as I have previously reported, I have communicated by mail with all of the Governors, urging them to organize Regional Meetings. I have had a large percentage of replies, some enthusiastic and some cautious, but there has developed considerable action as you have heard from President Paullin.

Since last October there have been three Regional Meetings—in Philadelphia, Chicago and Boston—all highly successful, and between now and next September seven additional Regional Meetings are scheduled—New Orleans, Washington, Great Falls, Kansas City, Columbus, Jacksonville and New York. The suggestion of the Board of Regents that Regional Meetings be stimulated has borne fruit.

In relation to the participation of Governors in the activities of the College, you might be interested in learning how many of our Governors are involved in the work of the Committee for War-Time Graduate Medical Meetings, which has been established and which is going through the process of organization. We shall have a group of twenty-four consultants in various categories of specialization, and on this Board of Consultants twelve Fellows from the American College of Physicians have been appointed. Among the Regional Committees, of which there are twenty-four, there are thirty-one Fellows of the College of Physicians as members. Of the Regional Committeemen, fourteen of the appointees from the American College of Physicians are Governors; from the Board of Regents, there are three on the Regional Committees. The activities of the Governors from now on must necessarily be confined or developed in the field of Regional Meetings and membership on the Committee on War-Time Graduate Medical Meetings.

(On motion of Dr. Griffith, seconded by Dr. Palmer and carried, the report of the Chairman of the Board of Governors was accepted.)

DR. GRIFFITH: In arranging our Regional Meeting for Kansas City, I invited the Governors of all participating States to come to Kansas City for a preliminary organization meeting. They all responded and we had an all-day session. It is a suggestion for future Regional Meetings that participating Governors be called into conference to create a better feeling and to impress them with the fact that they are making a contribution.

PRESIDENT PAULLIN: This is a wise suggestion. May we have the report of the Committee on ANNALS OF INTERNAL MEDICINE by Dr. Walter Palmer, Chairman.

DR. PALMER: The Committee on the ANNALS met at the College Headquarters at 4:00 o'clock yesterday. Dr. Barr was excused. The following matters were discussed and presented for your information and approval:

1. Mr. Loveland informed the Committee that our printers, the Lancaster Press, would have to increase the cost of printing the ANNALS, due to increased wages and other difficulties due to the war, from $1,000.00 to $1,100.00 above the present contract. The Lancaster Press suggested it would absorb the increase in cost up to July 1 if the College would authorize an increase at that time. This would mean that the College would have to look forward to an increase of $600.00 to $700.00 for the balance of the year and a further increase in 1944. The Committee recommends this increase be authorized.

(Motion to adopt this section of the report was made by Dr. Palmer, seconded by Dr. Griffith and carried.)

I should call attention to the fact that Mr. Loveland reports that Government regulations require that there be 10 per cent reduction in paper for 1943, but I understand that that will leave ample paper to publish in the ANNALS what we have planned. We shall hear from Acting Editor Clough later.

2. The Committee has encouraged Dr. Clough to publish a series of medico-legal papers sponsored by Dr. Hubert W. Smith of the Harvard Law School. This series will appear in the April issue.

3. The Committee recommends the granting of the request of a review journal in Buenos Aires the privilege of reviewing articles appearing in the ANNALS. This review journal is sponsored by reputable men as far as we know, not only in Buenos Aires but in several of the South American countries. It seemed to us that the request is quite in order and we would like approval of that recommendation.

(Motion to accept this section of the report was made by Dr. Stroud, seconded and carried.)

In closing this report, I would like to say that the Committee believes the College is particularly fortunate in having Dr. Clough to act as Editor in the absence of Dr. Pincoffs.

(Motion to accept the above report as a whole was made by Dr. Griffith, seconded by Dr. Coffen and carried.)

PRESIDENT PAULLIN: May we hear now from the Editor of the ANNALS, Dr. Clough.

DR. CLOUGH: I have only a few points to present for information. As far as material is concerned, we still have a fair supply. We have accepted for publication for July and future numbers seventy main articles and about fifty case reports. It would require a year to publish these case reports and the main articles would run for eight or nine months. As Dr. Palmer has reported, we shall have to cut down on the amount of paper we use, but assuming that this reduction is not taken care of by diminished circulation, it will mean only a relatively minor diminution in the size of the journal. It would still give us two hundred pages per number, one hundred fifty of which would be scientific material and fifty would be reserved for College News Notes, advertising and miscellaneous material. I think that will be quite adequate.

We contemplate devoting the June number entirely to the publication of papers presented at Regional Meetings or Postgraduate Nights. For the most part, these papers present relatively little in the way of new investigation, but many of them are excellent reviews and we felt justified in using one number of the ANNALS to bring out such material for its educational value.

The April number will be devoted to medico-legal articles. Many of these articles will be of general interest; some of them not so much of general interest, but on the whole they are a good series of articles.

One matter I referred to the Committee and Dr. Palmer has asked me to bring it up here for action. It is mainly to place the responsibility upon the Regents. When Dr. Smith approached me concerning these legal articles, he intimated some editorial compensation would be welcome. Such action has not been customary in the past.

PRESIDENT PAULLIN: Before a motion is made, may we hear from Mr. Loveland about the circulation of the ANNALS.

SECRETARY LOVELAND: I predicted at the last meeting of the Board of Regents that we might have a definite shrinkage in circulation, but said that we would make an extra effort to promote circulation among non-members; also to increase our advertising volume in order to keep up the income. With 1370-odd members in the Armed Forces with waiver of dues, the circulation naturally would be greatly curtailed. However, I am pleased to report that there has been a surprising number of Service doctors who have waiver of dues but who desire to continue receiving the ANNALS

and have subscribed to it at the cost price. Furthermore, the offices of the Surgeons General have sent in numerous subscriptions for the large Army and Navy hospitals, with the result that the circulation is keeping up very well. A year ago, the March circulation was 5,822 copies, whereas the March circulation for this year was 5,750 copies.

With regard to the advertising, there has been a slight shrinkage—possibly one and a fraction pages per issue.

PRESIDENT PAULLIN: You have heard the supplementary report by Mr. Loveland. The report of Dr. Clough is before you for consideration.

(Motion that no honorarium be granted for the medico-legal material for the April issue was made, seconded and carried.)

PRESIDENT PAULLIN: Next is the report of the Treasurer, Dr. William D. Stroud.

DR. STROUD: The Auditor's Report and the Statements of Operation for 1942 reveal that there was a balance to surplus of $27,988.83, somewhat in excess of any previous year since 1938. The total Funds of the College, as of December 31, 1942, were:

Endowment Fund	$136,329.06
General Fund	190,569.76
	$326,898.82

The College has invested at book value, as of March 31, 1943, $252,536.68, the cash value at this date of which was $254,430.00, or an appreciation of $1,893.32.

A condensation of the Statements of Operation will be published in an early issue of the ANNALS.

(Motion to accept the Treasurer's report was made by Dr. Griffith, seconded and carried.)

PRESIDENT PAULLIN: Next is the report of the Committee on Finance by Dr. O. H. Perry Pepper, Chairman.

DR. PEPPER: The Finance Committee of the American College of Physicians met at the College Headquarters on April 3, 1943, with Drs. Charles T. Stone and O. H. Perry Pepper of the Committee, Dr. William D. Stroud, Treasurer, and Mr. E. R. Loveland, Executive Secretary, present. Dr. James D. Bruce was not present.

The Committee begs to report the following items:

1. In 1942 there was added to the

Endowment Fund	$ 3,742.68
General Fund	24,246.15
Total	$27,988.83

This is better than was expected.

2. The Budgets for 1943, as adopted at the December, 1942, meeting of the Board of Regents showed:

Anticipated Income	$82,410.00
Anticipated Expenditures	78.065.00
Anticipated Balance	$ 4,345.00

There has developed nothing which changes these estimates, except in two items.

3. At the December meeting, the Regents appropriated $2,500.00 for Regional Meetings, it being estimated that ten meetings at $250.00 each would be adequate.

The Executive Secretary now reports that two items have been higher than expected:

a. Printing of programs in a number sufficient to distribute to all Army and Navy Officers in the district;
b. Traveling Expenses.

The Finance Committee therefore recommends an additional appropriation of $1,000.00 for this purpose.

4. Since the Budgets were approved, an increase in wages to printers has raised the cost of production of the ANNALS.

The Finance Committee therefore recommends that an additional $1,000.00 be appropriated to the ANNALS, this being the amount requested by the Committee on the ANNALS OF INTERNAL MEDICINE.

5. There is now in the Endowment Fund cash equalling $5,195.99. Drexel & Co. recommends the purchase of 5 U. S. War Bonds, Series "G," paying 2½%. The Endowment Fund already holds $76,400.00 of Government Bonds and no common stock.

The Finance Committee voted to request Drexel & Co. to consider the investing of this sum in common stock.

6. The Finance Committee reports that the College has established its status as non-resident tax free in Canada with regard to securities, and has had refunded to it $55.00, representing 15% tax imposed on past dividends on the International Nickel Co. of Canada stock.

7. The Finance Committee is satisfied with the financial status of the College and begs to point out that if the two appropriations recommended in the report are made, it will have an anticipated balance for 1943 of $2,345.00.

(Motion to accept the report of the Committee on Finance was made by several, seconded by Dr. Cocke and carried.)

PRESIDENT PAULLIN: We need to appoint a successor to Dr. Harry B. Wilmer, deceased, to the House Committee. The present members consist of Drs. William D. Stroud and T. Grier Miller.

DR. PEPPER: I nominate Dr. Charles Brown, Professor of Medicine at Temple University.

(The nomination was seconded and carried.)

PRESIDENT PAULLIN: Next I have a letter addressed to me, being a resignation from Dr. O. H. Perry Pepper as Regent of the College.

(Dr. Pepper leaves the meeting.)

(Dr. Paullin reads letter.)

Gentlemen, if you would permit the Chair to make a few comments, I think Dr. Pepper's action can be applied to all of us, who have been asked to continue to serve in one capacity or another. Personally, I feel very deeply that at this particular time the College has an opportunity of accomplishing one of the greatest jobs that it ever will be permitted to do again, and it is through the advice and counsel and work of such men as Dr. Pepper and other members of the Board of Regents that we are going to be able to accomplish that purpose. I do hope that the Board will not accept this resignation.

(Motion not to accept the resignation of Dr. Pepper was made by Dr. Cocke, seconded by Dr. Griffith and unanimously carried.)

(A messenger asked Dr. Pepper to return to the meeting.)

PRESIDENT PAULLIN: Dr. Pepper, I am directed by the Board of Regents to inform you, Sir, that under no circumstances would they consider accepting your resignation.

DR. PEPPER: I appreciate that, but I wanted to give a chance to some of the men

serving the College, not yet recognized, to be placed on the Board of Regents, but I assure you I shall continue to do what I can.

PRESIDENT PAULLIN: Gentlemen, the next item, I think, is one of the greatest of interest to the College. It has to do with the matter that I briefly referred to in my opening remarks, to war and post-war planning of the College. Dr. Bortz, would you like to discuss the Regional Meetings together with the present method that you have established, namely, the War-Time Graduate Medical Meetings, with Dr. Breed and Dr. Blalock, or would you like to take up the matter as a whole?

DR. BORTZ: Mr. Chairman, the Regional Meetings of the College during the past few years have been increasingly successful as disclosed by the interest and attendance on the part of members. When war clouds began to gather and it became evident that our Nation was going to become involved, the leaders in American medicine wanted to play a just rôle and take their responsibility in providing the medical supervision that was imminent in the action to come. In certain sections of the country overtures were made to commanding officers of military installations to the end that the College might put on a series of courses of instruction in their hospitals. Here in Philadelphia we contacted the commanding officer of the Naval Hospital and asked him whether the staff of the hospital would be interested in having the American College of Physicians put on a series of graduate nights. He discussed the matter with the staff and it was enthusiastic about such a proposition. That was more than a year and a half ago. We have in Philadelphia a splendid group of teachers who was very glad to go to the Naval Hospital and conduct this series of Postgraduate Nights. All members of the hospital staff attended, and they were so pleased with the course that they immediately asked that another be given as soon as possible. A similar activity was developed in the Chicago area and the same experience was had there. Now, wherever the College has taken the leadership in putting on these courses they have been substantially successful.

The College Regional Meetings, let me point out, are at present being held in the metropolitan areas, for example, in Washington, in New Orleans, in Kansas City, in Columbus and elsewhere—in each area there is already a concentration of expert medical talent.

It seemed to the officers of our College, to the American Medical Association and to the American College of Surgeons that a movement in the direction of the military installations away from the metropolitan areas is needed. There is a greater need for teaching in the medical installations away from these centers and that, in essence, was the motivating idea behind the creation of the Committee appointed by Drs. Paullin, Abell and Rankin to instrument these War-Time Graduate Medical Meetings.

For purposes of organization and action, the country has been divided into 24 different areas and for each of these areas there is a working committee of 3 doctors, one to represent the American College of Physicians, one the American Medical Association and one the American College of Surgeons.

In addition, about ten days ago in New York City, Drs. Paullin, Abell and Rankin appointed a group of 23 national consultants, a Board to act in a consulting capacity for the purpose of selecting men to go into the military installations for purposes of teaching. Also, each of these consultants is asked to draw up a key program that may be used wherever these programs are conducted at military installations.

Before the personnel of the Board of National Consultants was selected a far-reaching study of the various men in the various special fields was made by the directing heads of the three organizations, and these organizations then selected the following men to make up the Board of National Consultants, all of whom have a national reputation, widespread contacts, years of experience in various special fields and who have the ability to procure the services of the other men who will be called upon to coöperate in this program.

(Dr. Bortz read list of Consultants.)

The list of the men on the Regional Committees is too long to read, but we have an outstanding group of men who will act on the various Committees throughout the entire Nation.

We shall send a copy of the preliminary announcement to all members of the Board of Regents and to the officials of the three participating organizations. The program, in brief, is an endeavor to carry into the camps away from the metropolitan areas a group of top-flight teachers to conduct teaching ward rounds, clinical pathological demonstrations or to use motion pictures, for instance, in the venereal disease field. They may conduct conferences, seminars or anything that the commanding officer and the teachers desire. Visualize, if you will, a group of six hospitals in an area like eastern Pennsylvania. One day we shall send a team of two or possibly three men to conduct teaching rounds, one day from 10:00 to 12:00 in the morning and from 2:00 to 4:00 in the afternoon. They may use movies and have question and answer periods. From 7:00 to 9:00 in the evening they may conduct another question and answer period or give a lecture. Monday of the next week they may go to another hospital and the following Monday to still another hospital in the area, and so on until they have made the rounds of the four or five installations assigned to them.

On Tuesday of each of the weeks a second team in another field will conduct programs, moving along each week from one installation to the next and so on through the week. In that way no individual will be asked to give more than one day a week for a series of four, five or six weeks, approximately twice a year, to this teaching program.

The movement is a worth while one if we can judge from the enthusiasm that has been voiced on the part of practically every individual with whom it has been discussed. However, last evening an adverse comment was voiced by one of the men who is acting as a National Consultant who expressed doubt whether men of the caliber desired would have time and could be persuaded to join in this movement, but let me point out this fact to you, gentlemen, that already this particular teacher is heavily engaged in a teaching program. He is already going from camp to camp. Other highly competent men have been recklessly generous with their time in visiting hospitals away from the metropolitan areas. This movement is merely an attempt to systematize and make more effective the magnificent work they are already doing.

We have three of our national organizations behind this movement, the American Medical Association, the American College of Physicians and the American College of Surgeons. Although there has been no publicity as yet, other societies have written in and requested that their names be attached to the group of sponsors.

When Dr. Byrl Kirklin was selected as one of the National Consultants he said he would immediately start to organize the radiologists of the country, ready to go anywhere the Committee wishes to send them. A similar opinion was voiced by Dr. Edward Strecker of the American Psychiatric Association and by Dr. Ralph Pemberton of the American Rheumatism Association. Dr. Pemberton said this movement is one of the most significant developments in teaching of medicine today, that it is a great opportunity and he considers it a real privilege to participate.

It appears that there is a place for such a movement and that there will be an adequate number of qualified teachers who will be willing to suffer the inconvenience of going to these military installations to instruct these younger doctors. In this way they will be playing a very real rôle in the war effort, a rôle that has been denied to a good many of our teachers because they are over-age or have some slight physical limitation or because they are regarded essential on teaching faculties.

Some time ago in Chicago Dr. Irons and I visited the offices of the Council on Medical Education and Hospitals of the American Medical Association and Dr. Weiskotten has written to the deans of the medical schools throughout the country concerning this project. We are just beginning to get reports from the deans, and

they are eager to place their faculties as far as possible at the command of this Committee for the purpose of organizing the personnel for giving these courses.

We expect to have a teaching medical faculty on a national scale, a great pool of the finest medical talent that the country has to offer, under the supervision of nationally known consultants in the special fields, implemented through well-chosen representatives acting as local committees in the twenty-four different areas. We believe we have a new instrument here, created for the purpose of mobilizing the teachers of medicine in this country to help the medical men of the Armed Forces in a most effective manner.

A number of teachers have expressed the opinion that this activity will be of equal importance with that of the instruction of undergraduates in the medical school.

I may say that the three Surgeons General have been kept informed about the activities all along the line and as soon as any new development comes along, information is sent them. We anticipate that the Surgeons General will draw the attention of their various commanding officers in Army and Navy hospitals to these programs. In that way we believe a prompt and enthusiastic response will be obtained.

PRESIDENT PAULLIN: May we also hear from Dr. Breed who is the representative on that Committee of the American College of Physicians.

DR. BREED: I have nothing specific to add.

DR. IRONS: This is a great opportunity for American medicine; it offers an opportunity to take the lead in this war-time activity and also for American medicine to work as a whole in questions which are bound to come in the post-war period. American medicine must take a more active and positive part in making plans for the post-war world. Things will be different than they were before the war. We might just as well recognize that. In those changes that are bound to come we must see to it that American medicine has its part in directing the kind of medical service that people are going to get. Here is our opportunity.

Mr. Chairman, I should like to hear from Brigadier Meakins.

BRIGADIER MEAKINS: Mr. President, we are faced in Canada with very much the same problems as you. Much of my present work evolved through my insistence there be plans for looking after the men in the Armed Services in the way of intellectual and professional instruction. Particularly do I fear the result of the acceleration of the undergraduate medical program and the curtailment of his opportunities, as they existed in peace time, for two to five years of postgraduate experience and practice under his superiors.

Some of the problems in our country are a little worse than yours. Our Army and Navy and Air Force are not comparable in size by any means. Many of our medical officers are scattered throughout the country in camps far removed from metropolitan areas. It is a great problem to keep up their professional morale. We are proceeding along three lines. We have appointed a corps of eight consultants whose duty it is to be on the road constantly, visiting each station, making rounds, discussing the problems, operating if necessary, introducing new methods of procedure and bringing aid to these men who have been in service over three years, who never have an opportunity to get back except on two weeks' annual leave, which should not be devoted to professional work. Many of these professional men at camps do not see the sick. The sick in the Army should be a minimum. It is the medical officer's job to see that the soldiers do not get sick. This is quite a reversal of the usual concept of the practice of medicine. The usual concept of the majority of our profession is not to pay very much attention to the individual as long as he is not a patient.

We were late in establishing a Procurement and Assignment Board. The name is exactly the same as yours and was copied. After a few months of its operation, it was found that it was not the scarcity of doctors that made the civilian hardships but the maldistribution of doctors, and that was due to a variety of causes. Dentists were badly distributed; faculties of medical schools were badly depleted; nursing service

was being disrupted. Many could not get a nurse although there were plenty of nurses had they been properly distributed.

The Procurement and Assignment Board, through the Minister of National Defense and the Privy Council, was instructed to make a survey of all the medical and health requirements of the Dominion. There were very wide terms of reference, and not only will it cover the Armed Forces but also hospitals and their requirements, medical schools and their requirements, departments of health, provincial and federal. It will cover the nursing service, the dental service, the distribution of medical manpower in villages, towns and cities; in fact, all social agencies that pertain in any way to health.

You may have seen in the press a note that was laid on the table of the House of Commons, called the March Report, which is analogous but by no means identical to the Beveridge Report. The March Report contained a great deal of suggested legislation or suggested ideas for legislation which will undoubtedly bring to the fore very strongly health insurance and the provision of a first-class medical service and health service to the people, so far as it is possible for our country to give them.

We have inherent in our method of government what we call "Provincial rights," what you call "State rights." These rights are very jealously maintained and no matter how paternal and generous the federal government may be, each of the provinces has to be dealt with separately. That leads to complications when one is dealing with health problems, because health and disease are no respecters of rivers or artificial boundaries.

The question of post-war education for the medical profession has been agreed to. Any man who has had his usual course of education interrupted, including his postgraduate education in hospitals, shall have one full year's graduate education in medicine or any of its specialties at the expense of the federal government. This is as generous as we can afford. He will be given an adequate amount, I think about One Thousand Dollars a year, as allowance.

We are now trying to organize the hospitals so that they will have a plan ready when demobilization begins, the hospitals to take these men on as an increased number of residents; I think there will be a time when we will swing back to the regular course of medical study, that we shall then need these extra men even more than now. To find places for fifteen hundred to two thousand such young men will be a difficult job. We want to give them actual graduate study, not lip service. We are not now producing specialists. True, we are producing a few psychiatrists, but for the most part specialists now are not being trained. At the end of the war surgeons will be of the rough and ready kind of the front lines and what they have been able to learn in our military, naval and air force hospitals. You can talk at a person all you like, but it is the doing—good medicine and good surgery under supervision—that's the best way to train good men. Our local societies and our universities will each attempt this year to hold at least one, if not two, of what we may call postgraduate weeks, Monday through Friday, five days. Because we are so scattered, it is difficult to bring any volume of men together. We are hoping to stagger these meetings so as to send experienced men to take the places of those on leave to take these courses. The movement of men overseas also interferes, because their sudden movement as reinforcements may make them miss such opportunities. I am seeking to have such men, when they are warned for overseas duty, to be sent at Government expense, on pay and allowances, to take the next course available so that they shall not lose out altogether.

Mr. Chairman, it is very refreshing for me to hear what you are doing. It is helpful because we have the same problems and it is advantageous to see how other people are solving them.

DR. BREED: In the earlier days of the war, the Surgeon General allowed eighteen months between the time of graduation and induction into the Service of doctors, in

order to allow them a year's internship. Now they have changed that and reduced the number of months to twelve. It is obviously impossible to accommodate all of these boys with a twelve month internship when only twelve months are allowed between graduation and time of induction, and it seems to me that the Surgeon General's Office must change that back to eighteen months or the hospitals will have to contract their term of internship to nine months. . . .

PRESIDENT PAULLIN: For your information, through the Committee on Allocation of the Procurement and Assignment Agency, in coöperation with the War Participating Committee of the American Medical Association, representations have been forcibly made to the Surgeon General and to the Secretary of War concerning the situation Dr. Breed has just outlined. The present status is: There will be no reduction in the time between graduation and induction. Men will have to begin their internships immediately after graduation at Government hospitals. If a man does not complete his one year of rotating internship, which they much prefer, or his one year in medicine, he will be given an opportunity under the present set-up to finish his three extra months in some hospital approved for internship in some other part of the United States. If he does not wish to take this, he will be accepted in the Army or in the Navy and allowed to complete his internship in one of these hospitals.

DR. BREED: That means that most of the hospitals will have to reduce their internship terms to nine months.

PRESIDENT PAULLIN: That is correct. They will not necessarily have to do so; if they can take care of an increased number of interns and give them proper training, they may keep them for twelve months; but they have got to give these interns adequate training—an adequate number of patients to supervise. There are many hospitals in the United States approved for intern training but without interns. Hospitals in the larger cities have an abundance of material or interns; in fact, too many. We hope to distribute to these approved hospitals where interns will get adequate training, some interns who will be available for a year.

DR. BORTZ: Mr. Chairman, in Massachusetts the State Medical Society already has a very satisfactory program somewhat similar, in which they are sending teachers into the camps. Iowa also has a set-up of the same kind. Wherever State societies have already organized such a plan, it is not the idea of the Committee on War-Time Graduate Medical Meetings to supersede that but rather to work in coöperation. Where we can in any way assist in elaborating a better program, a unity of action will be preferable.

PRESIDENT PAULLIN: Do you also mean to make these courses available for civilians as part of the program?

DR. BORTZ: That is right.

BRIGADIER MEAKINS: What solution has been arrived at as to the resident staff beyond the intern staff?

PRESIDENT PAULLIN: Approximately 20 per cent of the graduates in medicine of the six thousand graduates per annum will have physical disabilities that will keep them out of the military service, this 20 per cent including also women graduates. It is the hope of the Procurement and Assignment Agency to see that most of the resident staff of the hospitals is filled from this group or from others who are physically disqualified, already on duty. Through the Secretary of War and the Surgeon General of the Navy, we have an agreement at the present time by which they will allocate to us, the Procurement and Assignment Agency, a certain number of men who have already completed one year of internship, provided we can establish the essentiality of those men either as assistants in teaching or in rendering necessary medical service to a civilian community. Certain of these men at the present time can be deferred by Selective Service because they are married and have a family and dependents. That is not, however, a very large group.

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AMERICAN COLLEGE OF PHYSICIANS, INC.

BALANCE SHEET, DECEMBER 31, 1942

General Fund

Assets			*Liabilities*	
Current:			*Current:*	
Cash in banks and on hand		$ 21,588.71	Accounts Payable	$ 115.60
Notes Receivable		30.02	Deferred Income:	
Accounts Receivable:			Advance Subscriptions, ANNALS OF INTERNAL MEDICINE	14,736.64
Due from Brokers	$ 1,082.38			
Advertising	892.84		Total Current Liabilities	$ 14,852.24
American Air Lines	425.00	2,400.22		
Inventory of Keys, Pledges and Frames, at cost		422.80		
Accrued Income on General Fund Investments		290.00		
Accrued Income Due from Endowment Fund Income Account		1,192.91		
Investments at Book Value		116,118.61	Directory Reserve Fund	2,500.00
Insurance Deposit		555.00		
Total Current Assets		$142,598.27		
Deferred:				
1943 Postgraduate Courses		337.14		
Fixed:				$ 17,352.24
College Headquarters, Real Estate	$57,728.45		General Fund, as annexed	190,569.76
Less, Allowance for Depreciation	6,000.00	51,728.45		
Investment, Real Estate, 404–12 S. 42nd Street		9,170.50		
Furniture and Equipment, at cost	11,067.33			
Less, Allowance for Depreciation	6,979.69	4,087.64		
		$207,922.00		$207,922.00

Endowment Fund

Assets		*Liabilities*	
Cash in Banks	$ 214.11	Endowment Fund, Principal	$136,329.06
Due from Brokers	10,096 88	Accrued Income, Due to General Fund	1,192.91
Accrued Interest	1,192.91		
Investments at Book Value	126,018.07		
	$137,521.97		$137,521.97
TOTAL ASSETS	$345,443.97	TOTAL LIABILITIES AND FUNDS	$345,443.97

DR. FITZ: Mr. Chairman, I can remember the first time I attended a meeting of the College. I was struck with the youth of the College itself and I am wondering if some method can be devised through Dr. Bortz' Committee—some method by which we can make the College more attractive to young men. It is interesting to note that of the total number of members of the College we should now have almost 27 per cent in the Armed Forces. If you take one hundred forty thousand as being the number in the medical profession and then take 27 per cent of that, it will give you about thirty-eight thousand, which is about the number of medical officers as a whole in the Armed Forces. Applying this same percentage to the seventy-seven hundred Massachusetts doctors, again you get the figure of about two thousand, which is what we have in the Armed Forces. If you break down the figures of candidates for Fellowship and Associateship, again you get the same thing.

Most of the candidates for Fellowship are too old to go into the Army and Navy, but when you examine the candidates for Associateship, you get the younger men and a higher proportion are in the Armed Forces. All this makes me wonder, with the beautiful scheme you have described of postgraduate education, if we cannot take into consideration means of making membership in the College more attractive to the younger men. The postgraduate set-up ought to be directed to the young man rather than the older man.

PRESIDENT PAULLIN: The actual number of men in the College doing war work is not limited. Are there any other remarks?

In closing this session, I should like to thank Mr. Loveland, Mr. Hegland, Miss Ott and the others for their timely and beneficent help and again the Board of Regents for their untiring and unselfish devotion to duty as evidenced by the attendance at this meeting.

The meeting is adjourned.

Attest: (Signed) E. R. LOVELAND, *Secretary*

GENERAL FUND

OPERATING STATEMENT

For the Year Ended December 31, 1942

Balance, January 1, 1942		$166,323.61
Less:		
Transfer to Endowment Fund of the Initiation Fees of Life Members	$ 550.00	
To close Accounts Receivable for Advertising Uncollectible	41.40	591.40
		$165,732.21

Summary of Operations for the Year Ended December 31, 1942:

Income:		
Annual Dues	$27,982.16	
Initiation Fees	18,294.37	
Subscriptions, ANNALS OF INTERNAL MEDICINE	32,597.81	
Advertising, ANNALS OF INTERNAL MEDICINE	10,895.97	
Income from Invested Funds, General	4,414.73	
Income from Invested Funds, Endowment	4,564.12	
Exhibits, 26th Annual Session	12,987.97	
Guest Fees, 26th Annual Session	498.00	
Profit on Keys, Pledges and Frames	240.42	
Profit on Sale of Investments, net	91.10	
Dividend on Perpetual Insurance Deposit	60.00	
Sale of 1941 Directory and College History	59.24	
TOTAL INCOME		$112,685.89

Expenses:				
Salaries			$30,617.45	
Postage, Telephone and Telegraph			4,419.75	
Office Supplies and Stationery			1,337.86	
Printing			24,968.73	
Traveling Expenses			5,256.28	
College Headquarters:				
Maintenance	$2,156.05			
Heat, Light, Gas and Water	704.84			
Taxes	859.57			
Insurance	121.50		3,841.96	
Depreciation on Building, Furniture and Equipment			1,863.31	
Grant to National Research Council			697.16	
1942 Directory Supplement			425.26	
Directory Reserve, 1943			2,500.00	
John Phillips Memorial Prize			262.75	
Research Fellowships			3,600.00	
Investment Counsel and Custodian's Fee			413.89	
Regional Meetings			1,305.46	
Postgraduate Courses			996.64	
Investment, Real Estate, net			687.03	
Other Expenses:				
26th Annual Session	$3,536.01			
Miscellaneous	1,118.80		4,654.81	
TOTAL EXPENSES				$ 87,848.34
Net Income for the Year Ended December 31, 1942				24,837.55
Balance, December 31, 1942				$190,569.76

ENDOWMENT FUND

OPERATING STATEMENT

For the Year Ended December 31, 1942

Principal Account, January 1, 1942			$132,586.38
Add:			
Life Membership Fees received during 1942	$2,508.00		
Transfer of Initiation Fees of New Life Members from General Fund	550.00		
Gain on Investment Transactions, net of Losses	684.68		
Total Increase during 1942			3,742.68
Principal Account, December 31, 1942			$136,329.06
Income Account:			
Income from Investments earned during 1942			$ 4,564.12
Deduct:			
Research Fellowships	$3,600.00		
John Phillips Memorial Prize	262.75		3,862.75
Excess of Income over Expenses, transferred to General Fund Operations for 1942			$ 701.37